NUTRITION AND THE CLINICIAN *

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THE distinction between nutrients and foodstuffs is important. Oxygen, water, and the common electrolytes are all strictly speaking nutrients but by convention are usually excluded from that term. The nutrients, as ordinarily referred to, include carbohydrate, fat, protein, vitamins, and inorganic elements. Certain of the latter are present in foodstuffs as trace elements—e.g., iodine. Carbohydrates, fats, and proteins are, of course, all variable combinations of simpler nutrients such as glucose, fatty acids and glycerides, and aminoacids. Confusion is often caused by failure to recognise in terminology that protein, as referred to by dietitians, is both a combination of aminoacids and the vehicle of other nutrients. I have therefore made a practice for some years of referring to the dietitian's concept of protein as " protein-rich foodstuff " (by contrast the word food is ordinarily used to indicate a mixture of foodstuffs which appeals to taste and satisfies hunger).

The term " foodstuff " is defined as " anything which can be used as food " (*Oxford English Dictionary* and *Webster*). In urban civilisation foodstuffs may be fresh or preserved, natural or processed. Natural foodstuffs may contain poison (e.g., synecio, causing bread poisoning), pesticides (arsenic, parathion), or pathogenic micro-organisms (salmonellæ, brucellæ, *Mycobacterium tuberculosis*). Foodstuffs may become contaminated during distribution (streptococci, staphylococci). They may become poisoned by preservatives (boric acid) or lose nutrients by spoilage (vitamin C). Processed foodstuffs may lose nutrients in the course of processing (vitamin B_1 in white bread) or be altered in chemical form (hydrogenation of oils). Losses of nutrients during processing may be made good by industry and commerce with or without legislation (synthetic thiamine [aneurine] in white rice and white bread). Foodstuffs may also be used as vehicles for enrichment or fortification with nutrients which may be deficient in the total diet (e.g., the incorporation of milk powder or soy-bean flour in bread).

Nature and Nurture in the Ætiology of Human Disease

Fig. 1 (Brock 1948) is intended to stress the principle of multiple ætiology in human disease, the progressive development of constitution by interaction between genotype and environment, and the shorter-term relationship of disease to constitution. Environmental factors are divided into health-promotive factors and the external agents of disease. A healthy constitution is developed by a favourable balance of health-promotive factors over external agents of disease but is grounded in the genotype. Disease is produced by an unfavourable balance between health-promotive factors and external agents of disease, the latter acting more readily on an unhealthy constitution but capable of causing disease even in a healthy constitution; ultimately, if their action is prolonged, they may result in the undermining of constitution.

The concept of constitution built around fig. 1 puts in different language rather similar thoughts expressed by Trowell (1951) under the term " life-flight " and by Gillman and Gillman under the term " life-track."

This diagram is of basic importance in teaching the principles of clinical medicine and medical practice. Its relevance to my present theme is in the relation between food, constitution, and disease. Food is one of the fundamental or elementary health-promotive factors, and without an optimum diet a healthy constitution cannot be built or maintained. Malnutrition and disease may result solely from deficient diet (unifactorial) but are commonly multifactorial—i.e., due to multiple disturbances of the normal relationships expressed in fig. 1.

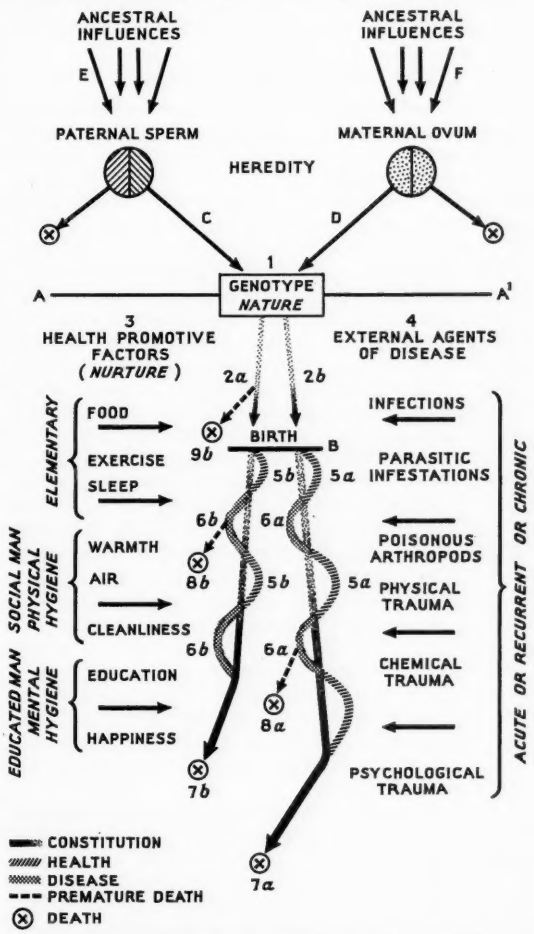

Fig. 1—Diagram illustrating relationships between genotype and environment, both favourable and unfavourable, in determining the development of constitution and life expectation, and of experience of health and disease.

The long-term progressive development of a healthy and of an unhealthy constitution is shown in the vertical straight lines; the short-term experiences of health and disease are shown in the sinuous deflections about the straight lines. (From Brock 1948.)

* The first Humphry Davy Rolleston lecture for 1959, delivered before the Royal College of Physicians of London on June 24. The second lecture, with the references, will appear in a forthcoming issue.

Recently attention has been directed among privileged communities to the adverse effects of excess of food or of various nutrients—i.e., obesity from caloric excess and possibly ischæmic heart-disease from consumption of excess fat or wrong balance between various qualities of fat (e.g., saturated and unsaturated).

Nutrition and Feeding

The concepts in fig. 1 are necessary for the construction of a working definition of the term " human nutrition ". The simple phrase " those aspects of structure and function which are particularly dependent on proper feeding " is put forward as useful to the physician. In terms of the above diagram it is only a relative definition, since in the last resort all structure and function are dependent upon proper feeding, and " optimum health " becomes dependent upon " optimum feeding ". The terms health and nutrition are not, however, coterminous; the former, although it depends on the latter, depends at the same time on many other factors. The consideration of many factors, as exemplified in the diagram, is necessary when examining some recent evidence from geographical pathology.

Geographical Pathology

When I returned to live in Cape Town I realised that Nature had provided a unique natural experiment which needed to be exploited. It consisted in the juxtaposition of three racial groups living in the same well-localised geographic and climatic environment but differing markedly in their socioeconomic status and in the incidence of undernutrition, malnutrition, and " social diseases " such as tuberculosis, syphilis, and infantile diarrhœa.

Of the two non-European racial groups, one—the Cape Coloured people—had followed for more than a hundred years the cultural and dietetic pattern of the European, and differed in no radical sense from the equivalent pattern of the underprivileged European (Brock 1949). The other group—the Bantu—came from a rural pastoral background in which the cultural and dietetic pattern is vastly different from that of the European. Very few of the Bantu have been urbanised for more than a generation, and the great majority are migrant labourers returning to their homes after living for a year or two in the city (Brock 1959c). These migrant labourers retain to a very large extent the cultural and dietetic background of their home environment, while their urbanised brethren—a small minority—are slowly trending towards the European pattern.

There is obviously a remarkably opportunity to study the respective effects of the genotype and of the social and economic background in determining the very different patterns of morbidity and mortality. Our efforts to use this opportunity have proved as rewarding as many intensive laboratory experiments.

Interracial studies and studies in geographical pathology in Africa lead to fascinating speculations about the role of malnutrition in general, and of protein malnutrition specifically, in the ætiology of some diseases prevalent in tropical regions (Brock 1955a). This may be exemplified by considering the geographical pathology of kwashiorkor and primary cancer of the liver.

Kwashiorkor

This disease, the most serious and widespread nutritional disorder known to medical and nutritional science, has been reviewed elsewhere (Brock and Autret 1952, Trowell et al. 1954, Brock 1959a). It can be defined as a disease widely prevalent in underprivileged parts of the world, both within and without the tropics, where children are customarily weaned largely or wholly on starchy paps, without adequate addition of animal or protein-rich vegetable foodstuffs. There is a basic worldwide syndrome, modified by the type of starchy paps used and by other local variables. Children with the basic syndrome usually manifest (1) retarded growth; (2) hypoalbuminæmia, usually associated with œdema; (3) severe diarrhœa, often accompanied by electrolyte imbalance; (4) fatty infiltration of the liver; and (5) atrophy of the acini of the pancreas with reduction of the enzymatic activity of the duodenal juice. Additional features which may be present include a variety of dermatoses, dyspigmentation of the hair and skin, digestive disturbances, mental apathy, muscular atrophy, and anæmia. In the absence of proper dietary treatment the mortality-rate is heavy. On the other hand, when infants are treated with skim milk, prompt and complete recovery may be expected except in late or severely complicated cases.

In other reviews (Brock 1959a) it was concluded that the basic cause of kwashiorkor is dietary protein malnutrition; and, since a group of aminoacids constitute the " most-limiting nutrients ", it is in essence a state resulting from deficiency of nitrogen or imbalance of aminoacids in the presence of more generous intake of calories in the form of starchy foodstuffs.

Cirrhosis and Primary Cancer of the Liver

The world distribution of primary carcinoma of the liver was mapped by Berman (1951). In a survey of the world distribution of kwashiorkor Brock (1954) stated that when the two were compared they corresponded sufficiently to suggest some ætiological relationship, but there were also important regions of non-correspondence. Brock (1957) concluded that dietary deficiency probably plays a part in the ætiology of the adult cirrhosis which, in areas of high incidence, is the precursor of primary carcinoma of the liver. The ætiological role of tropical parasitism, though this is apparently not a major factor, cannot be entirely ignored. Attention has also been given to the possibility of chronic contamination of food with hepatotoxic alkaloids as a factor in the ætiology of so-called " nutritional cirrhosis ".

That adult " nutritional cirrhosis " arises from kwashiorkor as a direct and necessary sequel must be regarded as unlikely (Brock 1954, 1957), but the dietary pattern which produces kwashiorkor in some populations in Africa is at least one of the causes of high prevalence of adult cirrhosis and primary carcinoma of the liver. At the suggestion of J. Gillman, who had contributed much to ideas in this field (Gillman and Gillman 1951), a symposium on cancer of the liver among African Negroes was convened by the International Union Against Cancer in Kampala, Uganda; and the summary of its proceedings (Kampala Conference 1957) speaks of facts and circumstantial evidence " suggesting that prolonged dietary inadequacy may play an important role in injuring the liver, with subsequent appearance of primary carcinoma in some of the exposed individuals ". The conditions apparently associated with high rates of liver cancer are: inadequacy of the diet in infancy (as indicated by the development of kwashiorkor in young children), abnormal nutrition (often cyclic) over the entire life-span, and unusual exposure to various infections. In addition, there is evidence from experiments with animals that the foods and beverages consumed may contain toxic agents, or

possibly carcinogens, which would presumably be less injurious to the liver of people who were in a better nutritional state.

Although the term " protein malnutrition " was not used in the Kampala Conference summary, the reference to kwashiorkor at once raises this concept. Before it is discussed a little consideration is required of the term " protein-rich foodstuffs ".

Protein and Protein-rich Foodstuffs

If foodstuffs are expressed in terms of grammes of protein yielded per 100 calories (fig. 2) they fall naturally into two groups which can be called respectively low-protein and high-protein foodstuffs.

The low-protein foodstuffs include all the cereal grains yielding about 2–3 g. of protein per 100 calories—i.e., they are marginal for human protein requirements expressed in quantity. The roots and tubers all fall below 2 g. per 100 calories—e.g., cassava (manioc, arrowroot) flour yields under 20 g. of protein per 2000 calories.

Among the high-protein foodstuffs are animal products ranging from whole milk (5·5 g. per 100 calories) to dried fish (±15 g.). Since nuts and legumes fall within the same range as animal protein foodstuffs, the high-protein foodstuffs can be further subdivided into those of animal and those of vegetable origin (Brock and Autret 1952).

In the last decade, however, it has been increasingly recognised that to express protein requirements in quantitative terms alone is quite inadequate, and that the quality of protein is more important than its quantity. Quality of " protein " is dependent upon its aminogram or pattern of aminoacids. The United Nations Agencies, F.A.O. and W.H.O., are attempting to construct an ideal " reference protein " or aminogram which would meet the needs of the body for the essential aminoacids with the greatest economy of quantity. Until such a reference protein is universally accepted, milk is usually taken as the reference protein for human requirements, while whole egg is often taken as a reference protein for animal and particularly rat experiments.

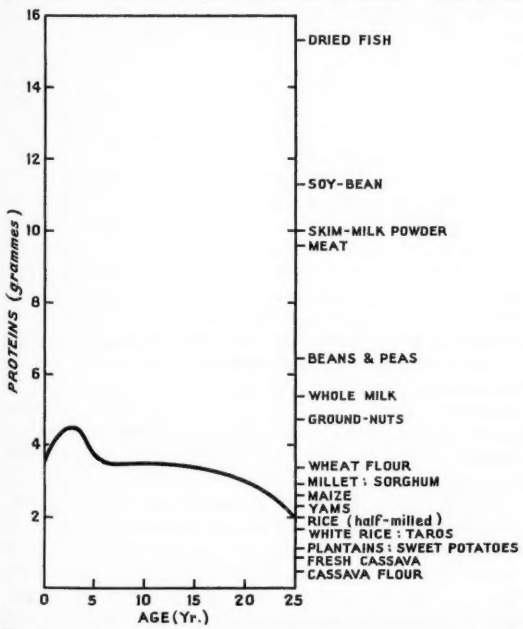

Fig. 2—Requirement of protein expressed in grammes per 100 calories at ages up to 25. The yield of protein per 100 calories from some common foodstuffs is shown at the right. (From Brock and Autret 1952.)

Much has been written about the possibility of improving the aminogram of protein mixtures by judicious combination of natural proteins or by supplementation with synthetic aminoacids (Flodin 1958).

Having discussed quality of " protein ", we must now reconsider " protein foodstuffs ". Their value will depend upon (1) quantity of protein (e.g., in relation to calorie yields); (2) quality of protein (aminogram); and (3) the content of other nutrients of all types. Especially important under (3) will be their content of vitamins and of certain minerals, particularly trace mineral elements. Thus by judicious combination it would be possible to construct two protein-rich foodstuffs, one of animal and the other of vegetable origin. But though they might contain the same total quantity of nitrogen in relation to calories, and very similar, if not identical, aminograms, the foodstuff of animal origin would contain vitamin B_{12} in good quantity, while the foodstuff of vegetable origin would be largely lacking in this vitamin.

Protein Malnutrition

The third Joint F.A.O./W.H.O. Expert Committee on Nutrition (1953) produced the following definition:

" In the fields of medicine, public health, and medical research, attention has recently shifted from disease due to deficiency of vitamins and minerals to what can provisionally be called protein malnutrition. This term cannot at present be defined within narrow limits. It is used here to indicate in general a state of ill-health occurring where diets are habitually poor in *protein*, while they are more nearly adequate in calories. Clinically, protein malnutrition is most easily recognized when there is a relatively high intake of calories from starchy foods together with an insufficient intake of protein. The concept includes the effects of deficiency in the quantity of protein consumed, of imbalance of amino-acids, and deficiency of factors, such as vitamin B_{12}, commonly found in foods in association with animal protein and concerned with protein metabolism."

This definition has led to some ambiguity, with resultant criticism, because the first unqualified reference to protein (italicised) should have read " protein-rich foodstuff " or " protein-rich foods ". It is quite clear from the term " starchy foods " farther down that this was the intention of the committee. The same intention is implicit in the last paragraph of the definition, which refers to amino-acid and " factors such as vitamin B_{12} ". In other words, it seems clear that the committee did not intend the term " protein malnutrition " to be synonymous with deficiency or imbalance of aminoacids alone (Brock 1955b). It was meant to denote a widely prevalent form of malnutrition due to deficiency in quantity of quality of " protein foodstuffs " and manifesting itself as deficiency or imbalance of aminoacids together with deficiency or imbalance of other nutrients including vitamins and minerals. This interpretation of the term " protein malnutrition " is vital to a consideration of the clinical effects of protein malnutrition and of other diseases widely prevalent in underdeveloped regions (Brock 1955a).

Protein malnutrition was again the subject of an international conference in 1957 (Waterlow and Stephen 1957).

Prevalence and Severity of Protein Malnutrition

That kwashiorkor is a manifestation of protein malnutrition as defined above is generally conceded. I would go further and say that it is an expression of aminoacid deficiency or imbalance. Our therapeutic trials with

synthetic mixtures have established that some pattern of aminoacid constitutes the most limiting nutrient or group of nutrients (Hansen et al. 1956, Brock 1959a). Undoubtedly deficiency of many nutrients besides aminoacids contribute to the ultimate clinical picture; but if the particular pattern of deficiencies of aminoacids can be identified and supplied in the diet of post-weaning children the syndrome of kwashiorkor will rapidly disappear.

With regard to the importance of protein malnutrition in the ætiology of diseases at older ages there is less unaniminity. Brock (1955a) concluded:

"If the central position of protein malnutrition in the ætiology of the chronic liver diseases of the tropical world is accepted then it becomes possible that protein malnutrition or some other type of malnutrition may be important or even central in the ætiology of some diseases of uncertain ætiology which are endemic in tropical areas and less commonly encountered in temperate areas. This may be speculation, but it is not idle speculation. As would be expected if chronic protein malnutrition were a widespread cause of ill-health, almost every system of the body is affected by diseases which are seldom if ever encountered in temperate climates and more privileged communities. It would appear that the scientific problems posed by recent concepts of the ætiology and pathogenesis of kwashiorkor need to be extended to cover the whole range of the mechanism and effects of chronic protein malnutrition."

Trace Elements in Human Nutrition

Protein-rich foodstuffs are important vehicles not only of essential aminoacids but also of essential vitamins and trace mineral elements.

The role of trace elements in biological nutrition (Davis 1957) and in soil economics (Schütte 1957) was reviewed two years ago, and their possible implications for clinical medicine this year (Brock 1959c). The 1952 edition of McLester and Darby's textbook says:

"The occurrence of deficiencies of trace elements in herbivora has fired the imagination of many as to the possibility of similar deficiencies occurring in man.

"Despite the considerable amount of loose and uncritical discussion of trace elements and their deficiency in man, particularly as related to the quantity of these elements present in soil, it may be fairly stated that, with the exception of iodine, no acceptable evidence has appeared for the occurrence of them in the soil."

Considering whether any evidence has developed since 1952 which would justify revision of this statement, Brock (1959c) concludes that the case for iodine deficiency is settled. The case for fluorine deficiency in relation to dental caries is accepted, and, where human diets are mainly or wholly derived from vegetable sources, a case may be built up in the future for cobalt deficiency. Both with fluorine and with cobalt the mechanism might be mediated through effects on bacterial flora in the digestive tract. The case for an internal or metabolic effect of deficiency of trace elements other than iodine has still to be made. This is perhaps not surprising as long as mixed diets are consumed, since flesh would probably not reach a development attractive to man's taste if it were seriously deficient in any nutrient. Iodine deficiency is, however, an exception to this argument, and there seems to be no reason why this one element should be the only exception.

Certainly evidence of the effects of dietary trace-element deficiencies should be looked for among vegetarian peoples, and particularly among vegans. On the other hand, internal deficiency might arise either from antagonism between trace elements and other inorganic constituents of the diet, or be conditioned by disorders of internal metabolism. Speculation about trace-element deficiency and its effects in man cannot be dismissed as ridiculous. The evidence for such effects should be examined very critically, however, because speculation is certain to outrun facts, especially in the case of diseases of unknown ætiology.

Though Barcroft's definition (1944) of the properties of "trace elements" can be accepted, the term is still ambiguous. The current list of medical literature lists under this heading Al, B, Co, F, Mn, Se, and Zn. In addition Cd, Cr, Pb, Ni, Rb, Ag, Sn, Ti, and V have been surveyed in healthy and pathological human tissues and magnesium and copper must be mentioned. In Brock's review special attention was given to the fascinating story of selenium (Schwarz and Foltz 1957, Schwarz 1959) in relation to factor 3 of the liver-necrogenic diet of Schwarz. In clinical medicine the role of iodine and of fluorine as trace elements has long been known, while copper and cobalt have an established place in theory. Man, however, seems to suffer seldom from deficiency of the latter two elements. Manganese and zinc have recently been discussed (*Nutrition Reviews* 1957, Vallee et al. 1957).

There is also a suggestion from a pilot experiment conducted in our laboratory that deficiency of trace elements in soils may affect the protein composition of plants. Beans grown experimentally on deficient media appear to have abnormal aminoacid patterns (Schütte and Schendel 1958). Such mineral deficiencies could therefore have an effect on health in areas where dietary protein is marginal and aminoacid deficiencies (kwashiorkor) occur.

Intestinal Bacterial Symbiosis

From the literature on trace-element deficiency it appears that effects on the host may be mediated by effects on the bacterial flora of the digestive tract (Davis 1957, Brock 1959c). This link brings us to a field of great potential importance. Since the early work on refection (Fridericia et al. 1928), it has been recognised that certain commensal microorganisms of the gastrointestinal tract may be capable of synthesising vitamins required by their host. The obvious corollary is that they may deprive their host of ingested vitamins and other nutrients. Attempts have been made to study this matter in germ-free animals (György 1958, Reyniers and Sacksteder 1958)—a most promising line of experiment.

The introduction of the broad-spectrum antibiotics and their use in man has emphasised another very important aspect of intestinal bacterial symbiosis, probably independent of its effect on vitamins. The disastrous staphylococcal enteritis which sometimes follows the use of broad-spectrum antibiotics, and the less dramatic but important monilial invasion which may also result, illustrate the value of intestinal commensal microorganisms in protecting the intestinal tract against invasion by pathogens.

The effect of penicillin on megaloblastic anæmias is also interesting. The macrocytic anæmias with megaloblastic hyperplasia of the bone-marrow are far more common in tropical than in temperate climates. One feature of the life of poor people in the tropics is their great dependence upon vegetable protein, which may lead to deficiency of vitamin B_{12}. Foy and Kondi (1954) have produced evidence that this type of anæmia can be improved by penicillin both by the oral and parenteral route. They

believe that the penicillin, in altering the intestinal flora, removes bacteria which compete for vitamin B_{12} or which inhibit other bacteria that synthesise vitamin B_{12}. It is interesting here to recall that cobalt is an essential constituent of the vitamin-B_{12} nucleus and that in ruminants deficiency of cobalt interferes with the synthesis of vitamin B_{12} in the intestine.

Another point of great public-health significance is the vicious-circle mechanism between malnutrition, gastrointestinal flora, and diarrhœa. In infantile summer diarrhœa culture of the stools often reveals no pathogenic organisms (Kahn 1957). Is this diarrhœa, so prevalent among the poor, itself the result of impairment of normal symbiotic relationships in the digestive tract as a result of malnutrition? There can be no question that it aggravates malnutrition and often precipitates kwashiorkor.

Drug, Antibiotic, and Vitamin

The introduction of sulphonamide drugs was soon followed by reports on their effects on vitamin-C excretion (Holmes 1943). Interrelationship was soon reported also, in both directions, between antibiotics and vitamins. Examples are the polyneuritis which followed the early use of the sulphonamide ' Uleron ', experimental seizures in man following the use of semicarbazide and other hydrazides and their prevention by pyridoxine (Pfeiffer et al. 1956), and isoniazid polyneuritis. Representative reviews have been made recently by Goldsmith (1956) and in a Conference on Therapy (1957). Merck Technical Service was able recently to list 102 references.

Conditioned Malnutrition

Malnutrition may exist in spite of a perfect diet. The intestine is a hollow tube in which food must be digested and from which nutrients must be assimilated, and after assimilation these nutrients have to be metabolised. Malnutrition in a person to whom a good diet is available is said to be conditioned by anorexia, or by gastrointestinal disorder, or by disorders of metabolism—e.g., from fever, infective disease, neoplastic disease, or endocrine disorders. These in turn may all result from dietary malnutrition. So a vicious circle mechanism may develop between defective diet and the gastrointestinal and metabolic conditioning mechanisms.

Results of Malnutrition

Malnutrition, whatever its cause or nature, leads first to disturbance of function and later to disturbance of structure. Acute malnutrition may be rapidly and completely reversible. As represented by hypoglycæmia, it may affect many tissues and organs and may express itself through disordered function of body, mind, and emotion. It is rapidly reversible on provision of the missing nutrient. Similar widespread, acute, and reversible manifestations can be seen in hypokalæmia and in thiamine deficiency, although a longer period of deprivation is necessary to exhaust body reserves. Can acute deficiency of nutrients cause irreversible functional and structural damage, on the analogy of the effects of anoxæmia on the myocardium or cerebrum? Certainly long-continued acute hypoglycæmia can cause irreversible cerebral damage. The same may be true of the effects of long-continued severe thiamin deficiency on the myocardium. Perhaps the most important effects of malnutrition, however, may be cumulative, and manifest themselves through a long-term effect on constitution (fig. 1) with resultant lack of resistance to infectious and other stresses and liability to degenerative diseases.

Recognition of Malnutrition and Assessment of Nutritional Status

In the later stages of structural disturbance from malnutrition careful clinical examination may be very revealing. The information yielded by height and weight is limited, because even in a homogeneous race a $\pm 10\%$ range must be allowed around the mean, on account of genetic variability. For the same reason overweight and obesity are not synonymous; nor are underweight and undernutrition. Assessment of subcutaneous fat by manual estimation of the double skin fold, or better with a skin calliper, can be used for estimation of body fat. The validity of skin-fold measurements has been established in man by deduction of total body fat from body specific gravity calculated by weighing successively in air and under water. The validity of the latter technique has been checked in animals by carcass analysis.

Many stigmata of malnutrition may be revealed by examination of the skin and its appendages and of mucous membranes (Jolliffe et al. 1950). Structural disturbances in internal systems may be revealed by radiology of the skeleton (e.g., for rickets); structural disturbance of the liver by liver puncture. Functional disturbance in the myocardium may be revealed by the electrocardiograph.

In the earlier stages of functional disturbance from malnutrition, identification of the cause may be difficult because of multiple ætiology (fig. 1). The diagnosis will depend on (*a*) history of defective diet; (*b*) exclusion of non-dietary causes by individual clinical and laboratory examination; and (*c*) biochemical identification of subnormal levels of nutrients in body fluids or excretions or of the presence of diagnostic metabolic abnormalities—e.g., blood pyruvate in thiamine deficiency. In the milder stages of chronic functional disturbance the only proof of malnutritional origin is the demonstration of better function after administration of the supposedly deficient nutrient or of a better all-round diet. I suspect that this type of subclinical malnutrition is a common cause of impaired vitality and growth in the economically depressed strata of all society and perhaps almost universally in underprivileged nations. In its recognition the experienced doctor or nutritionist must use the largely subjective and non-measurable criteria of posture, stance, and physical, emotional, and intellectual reactivity to test situations. In experienced hands these criteria constitute valuable and sensitive measures of functional efficiency. If disease is excluded and dietary deficiency presumptively established, then improvement in any or all of the criteria as a result of test feeding can carry conviction though it does not constitute final proof. Any horse-owner, for example, uses a feed of oats for improvement of functional vitality (friskiness) in his horse.

It is at present difficult to recognise the long-term effects of malnutrition on the constitution, because the mechanisms are poorly understood. The advance of knowledge will probably bring new diagnostic methods.

Malnutrition from Deficiency, Excess, or Imbalance of Fatty Acids

In 1929 Burr and Burr described a new deficiency disease produced in the rat by rigid exclusion of fat from the diet.

Arild Hansen and his colleagues of Galveston, Texas, have for more than a decade been attempting to evaluate the role of essential fatty acid (E.F.A.) in infant feeding. They have demonstrated that infants fed a skim-milk diet

extremely low in fat and linoleic acid, though otherwise nutritionally adequate, regularly have frequent large stools, perianal irritation, and dryness, thickening, and desquamation of the skin (Hansen et al. 1958). We have ourselves seen develop in infants treated for kwashiorkor on skim milk a pattern of fatty acids in the serum (Schendel 1959) suggestive of E.F.A. deficiency.

From this I turn to the possible relation of excess or imbalance of dietary fat to ischæmic (coronary) heart-disease.

EPIDEMIOLOGICAL OBSERVATIONS ON HIGH BLOOD-PRESSURE WITHOUT EVIDENT CAUSE

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THE current controversy on the nature of high blood-pressure without evident cause can be summed up like this. In the general view, held since Allbutt's time, there is a specific disease of " essential hypertension ", and the population can be divided into those who have it and those who do not. Heredity has long been recognised as an important cause; and Platt (1947, 1959) believes that it is the main cause, the mechanism being a dominant gene with almost complete manifestation. On the other hand, Pickering and coworkers (Hamilton et al. 1954a, b, and c, Pickering 1955) postulate that blood-pressure levels are distributed " continuously " in the population and those with high pressures merely represent one extreme of this distribution: they are not a group apart, there is no disease entity of " essential hypertension " and to seek to define such an entity is misconceived. The inheritance of blood-pressure, it is suggested, like that of height and intelligence, is by multiple genes. Pickering believes, however, that most of the variation in blood-pressure levels is the result not of inheritance but of environmental factors as yet undefined. The object of this paper is to present further evidence on these important questions and to consider briefly some implications for clinical and social medicine.

Pickering's theory was developed from a series of studies carried out on hospital patients and their relatives (Hamilton et al. 1954a, b, and c). These studies show, for example, that in a sample of patients taken to be representative of the population as a whole the distribution curves of casual pressures were " continuous "—with only one mode or peak. (This is the sense in which " continuous " will be used in the present paper.) Pickering and his colleagues found no indication in the curves of the presence of two groups, one healthy and the other with a disease—hypertension. If there had been two such groups, curves which showed two peaks would be expected—so-called " bimodal " distributions. This absence of obvious bimodality is crucial in Pickering's theory.

Furthermore, Hamilton et al., in agreement with other surveys (for example, Master et al. 1950, Bøe et al. 1957), found that in population samples average blood-pressure levels rise with age. They interpreted this to mean that a rise of pressure with age is the rule rather than the exception and, in effect, is not pathological. Platt (1959) on the other hand, like Robinson and Brucer (1939), postulates that only those with the disease " essential hypertension " show a rising pressure. The rise in mean pressures with age in population samples, they suggest, is due to the emergence, as middle age advances, of increasing numbers of individuals with essential hypertension.

The opposing genetic theories are a necessary basis for the respective hypotheses about the nature of high blood-pressure without evident cause. Numerous studies have shown that inheritance has some influence on blood-pressure levels. If essential hypertension is a specific disease, the genetic element in it may be a single gene. If there is no *qualitative* difference between those with high and those with lower pressures, inheritance is probably multifactorial, by multiple genes (Hamilton et al. 1954c).

Pickering's theory has been received with considerable scepticism by others experienced in these questions, but no evidence was presented against it until recently. Platt (1959) reasoned that if, as he believes, essential hypertension is a disease " developing to a variable degree as the result of the inheritance of a major dominant gene or genes ", the middle-aged siblings of hypertensive subjects should segregate into those who inherited the disease from their parents and those who did not, and a bimodal (two-peaked) distribution of pressures would then be seen. He re-examined the data of Hamilton et al. and of Sobye (1948), and showed that blood-pressure distributions in siblings of hypertensives aged 45–60 were, in fact, bimodal.

The Study

In this unit we have data on the casual blood-pressures and the length of life of parents of a sample of the men working as drivers or conductors of London's buses and presumed to be healthy. This information was obtained during 1956–59 as part of a detailed clinical examination of these men in a study focused on cardiovascular and, in particular, on coronary-artery heart-disease of middle age. All the men were examined by one medical observer (Kagan 1959), and the blood-pressure readings cited in this paper are the " casual " readings taken sitting at the beginning of the examination before any personal or family history was elicited. Levels have been recorded to the nearest even number on the scale (though this presents its own problems with variation of the heart-rate) and there was no concentration of the readings at "tens" found in many surveys of blood-pressure. 302 men aged 45–60 will be reported. There are too few in the sample under 45, and, since there is evidence that an additional factor operates after 60 years of age, these men will be considered on another occasion.

In this sample there was only one possible case of secondary (renal) hypertension, in a conductor. There were no cases of malignant hypertension.

BLOOD-PRESSURE DISTRIBUTION OF THE BUSMEN

The data described have been used to test the opposing hypotheses about the nature of high blood-pressure, cause unknown. If parents are divided into hypertensives and normotensives, sons with a hypertensive parent will, according to the single-gene hypothesis, segregate into two roughly equal groups of normotensives and hypertensives, and the blood-pressure distribution curve of these sons will be bimodal. The sons of normotensive parents, on the other hand, will mostly be normotensive and show a continuous distribution of blood-pressures. According to the hypothesis of Pickering et al., the sons of

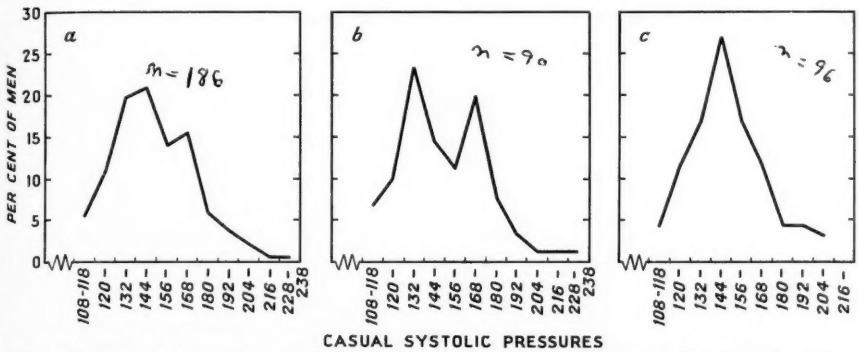


Fig. 1—Distributions of casual systolic blood-pressures in drivers aged 45–60 years: (*a*) all drivers (186 men); (*b*) drivers with one or both parents dead in middle age (90 men) (middle age = 40–64 years); (*c*) drivers with both parents living to old age (96 men) (old age = 65 years or over).

hypertensive parents and the sons of normotensive parents should both show continuous distributions; though the mean of the former distribution will be higher than the mean of the latter. We have no data on blood-pressure of the parents of the busmen. However, high blood-pressure is an important determinant of death in middle age. Patients with hypertension are known to die at younger ages than the general population. Fishberg (1954), for example, agrees with Weitz (1942) who found that "the maximum of the mortality curve for hypertensive patients occurs at an age about 10 years less than for normotensives"; Bechgaard et al. (1956) show that the mortality of hypertensives in middle age is about three times that of all men.

Bus Drivers

The systolic pressure distributions of 186 bus drivers are illustrated in fig. 1. Fig. 1*a* shows the distribution of all drivers; just over 5% of the drivers have systolic pressures between 108 and 118 mm. Hg, about 10% between 120 and 130, &c. Fig. 1*b* shows the frequency distribution of systolic pressures of drivers one or both of whose parents died in middle age; fig. 1*c* shows the distribution of drivers with both parents living to old age. In fig. 1*a* there is slight indication of a second peak. But fig. 1*b* is an obviously bimodal or two-peaked distribution with a break at about 160 mm. Hg between two groups of almost the same size. Men forming the first peak (at about 140 mm.) may reasonably be regarded as normotensive, and those forming the second peak (at about 175 mm.) as hypertensive. Fig. 1*c* shows a fairly normal distribution with a peak of about 150. The curve for *all* drivers (fig. 1*a*), with its hint of a second peak, seems therefore to be a combination of three quite separate distributions—that of normotensive drivers, of hypertensive drivers, and the group in fig. 1*c*. The slight discontinuity in fig. 1*a* is all that remains visible of the second hypertensive peak of fig. 1*b*, which

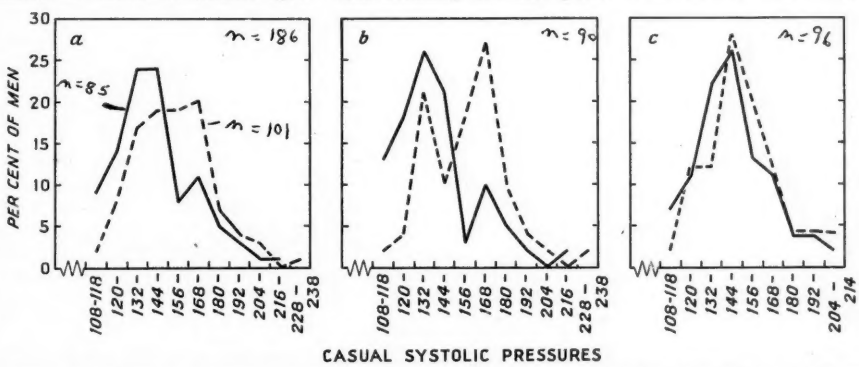


Fig. 3—Distributions of casual systolic blood-pressures in drivers aged 45–54 (continuous line) and 55–60 (interrupted line): (*a*) all drivers (186 men; 45–54 = 85 men, 55–60 = 101 men); (*b*) drivers with one or both parents dead in middle age (90 men); (*c*) drivers with both parents living to old age (96 men).

We propose therefore to divide the parents into those who died in middle age (40–64) and those living to old age (65 and over) on the assumption that this will give a crude subdivision into hypertensive and non-hypertensive groups or, at any rate, into groups with more hypertension and with less.

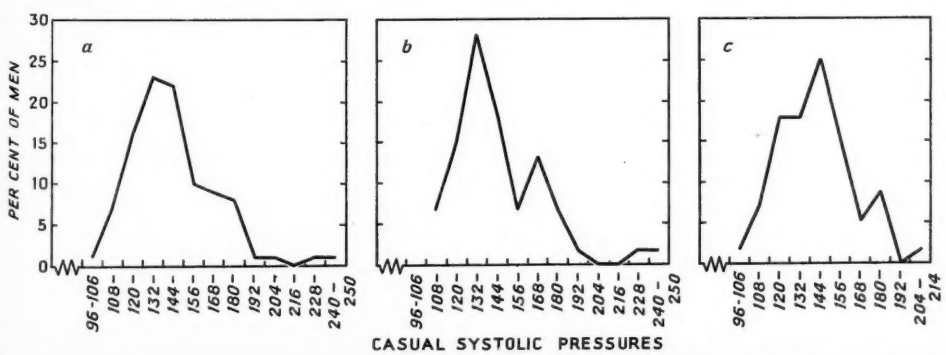


Fig. 2—Distributions of casual systolic blood-pressures in conductors aged 45–60 years: (*a*) all conductors (116 men); (*b*) conductors with one or both parents dead in middle age (60 men); (*c*) conductors with both parents living to old age (56 men).

includes perhaps 40 men, when this is merged in the mass of 186 men. The manœuvre of classifying by the length of life of parents has produced bimodality by exposing a hypertensive peak.

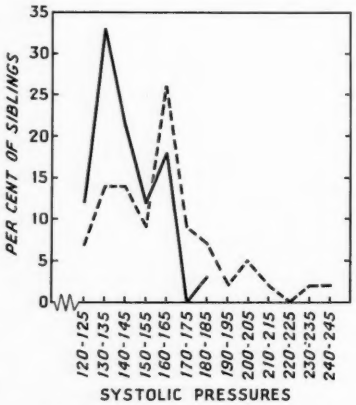


Fig. 4—Distributions of systolic blood-pressures in male siblings aged 40–49 (continuous line) and 50–60 (interrupted line) of male hypertensives aged 40–60 (Sobye 1948) (76 siblings; 40–49 = 33, 50–60 = 43).

Our data on *causes* of death of parents is of doubtful value. However, there is a strong suggestion that there were more deaths from cardiovascular causes among the parents of men forming the second hypertensive peak of fig. 1*b*, and fewer deaths from causes such as cancer and accidents than among the parents of men forming the first peak of the figure.

Bus Conductors

Distributions of systolic pressure of conductors, corresponding to those of drivers in fig. 1, are shown in fig. 2. There is a suggestion of a bimodal curve among the conductors whose parents died in middle age (fig. 2*b*), but the second hypertensive peak is smaller than in fig. 1*b*. It is notable that the two peaks or modes of this distribution are at the same pressure levels as in the drivers—140 and 175 mm. Hg. The curve in fig. 2*c* is not so regular as that in fig. 1*c* (numbers are smaller of course) but again this mode is at the same level—150 mm. Hg.

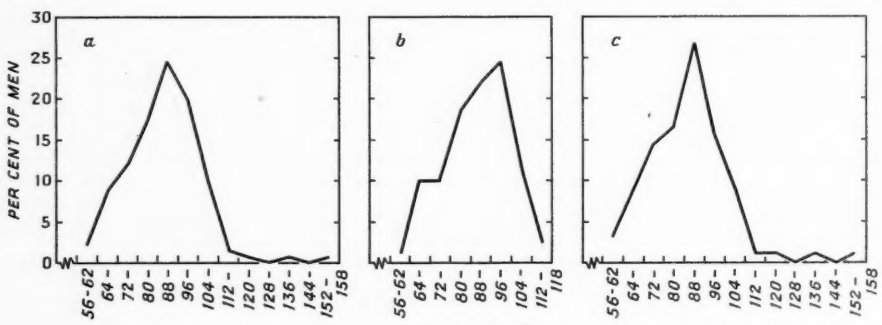
BLOOD-PRESSURE AND AGE IN BUS DRIVERS

The distributions of systolic pressures in fig. 1*a–c* are repeated in fig. 3*a–c*, but in each case now for drivers aged 45–54 and 55–60 separately. In fig. 3*a* the curve for all drivers aged 55–60 is wider than the curve at 45–54 and it has a higher mean value—158 compared with 147 ($p < 0.05$). In fig. 3*c*, among drivers whose parents lived past 65 years, there is little if any indication of a rise of pressure with age (mean values are 150 at 45–54 and 154 at 55–60, $p > 0.30$). Among drivers with a parent dead in middle age mean pressures increased from 144 at 45–54 to 162 at 55–60 ($p < 0.05$); in fig. 3*b* it can be seen that this increase is accounted for by the emergence of a notably larger second peak in drivers aged 55–60 with parents dying in middle age. There is a corresponding decrease in the first peak among these men. Moreover, there was no alteration with increasing age in the modal value of either the normotensive or hypertensive peaks in fig. 3*b*. In short the increase in mean pressures with age in fig. 3*b* is the result merely of the greater number of hypertensives in the older age-group among men with a parent dead in middle age.

Thus, nearly all the overall increase in the mean pressures of the whole group of drivers, from 147 at 45–54 to 158 at 55–60, is accounted for by the drivers whose parents died in middle age—and to the emergence among them of a large " hypertensive " group at 55–60. There is no evidence of any general shift in blood-pressure levels upwards within the age-span 45–60 among the drivers.

Bus Conductors

Analysis of the systolic pressures of the conductors in the two age-groups shows a similar (though less regular) picture to that of the drivers. Among conductors with a parent dead in middle age there are more hypertensive individuals at 55–60 than at 45–54; but not enough to raise the mean pressure of all conductors aged 55–60 (150) significantly above the mean at 45–54 (147).



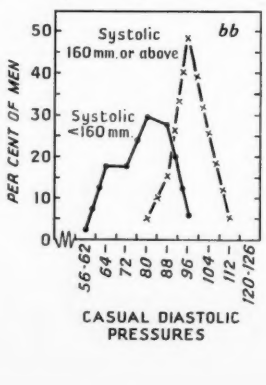


Fig. 5—Distributions of casual diastolic blood-pressures in drivers aged 45–60 years; (*a*) all drivers (186 men); (*b*) drivers with one or both parents dead in middle age (90 men); (*c*) drivers with both parents living to old age (96 men); (*bb*) drivers with one or both parents dead in middle age (90 men) (systolic pressures under 160, and 160 and over).

Siblings of Hypertensives

Some confirmation of this interpretation of the rise of mean pressure with age has been obtained from Sobye's (1948) data on siblings. Male siblings of Sobye's hypertensive male propositi aged 40–60 have been divided into two ten-year age-groups in fig. 4. As in our drivers, there is a small second peak in the systolic pressures of men aged 40–49, and this becomes much larger at 50–60. There is no indication of any rise in pressure with age among the presumably " healthy " men forming the left peaks of the two distributions.

DIASTOLIC PRESSURES

Diastolic-pressure distributions of drivers are plotted in fig. 5. The curve in drivers whose parents died in middle age is not bimodal (fig. 5*b*). However, if we accept the presumptive division between " normotensives " and " hypertensives " of fig. 1*b*—this is at about 160 systolic —we can divide the diastolic pressures in fig. 5*b* into

those of men whose systolic pressures are below 160, and those of men with systolic pressures of 160 and over. The result is shown in fig. 5*bb*. Apparently then, the continuous distribution of fig. 5*b* is made up of the two overlapping distributions of fig. 5*bb*. The break between these is at about 95 mm. Hg. The inclusion of a few men with comparatively low diastolic pressures in the right-hand distribution of fig. 5*bb* is interesting in view of the clinical impression that systolic reactions to 160 or 170 mm. Hg are the first stage of "essential hypertension".

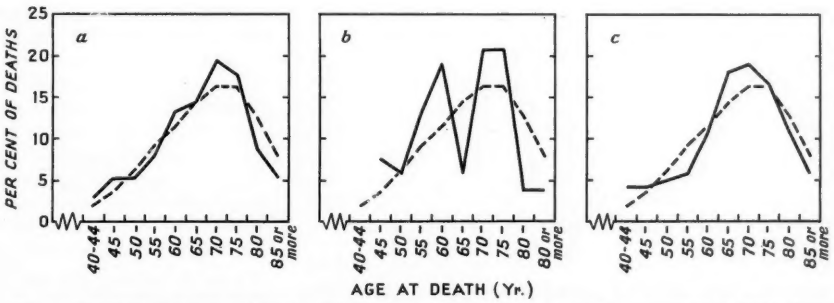


Fig. 7—Distribution of ages at death in fathers of bus drivers aged 45–60 years (percentage of deaths from all causes in each age-group, deaths under 40 years excluded. The interrupted line in this figure and in fig. 8 represents the distribution of ages at death of all men in England and Wales shown in fig. 6): (*a*) fathers of all drivers (174 deaths); (*b*) fathers of "hypertensive" (B.P. 160/95 mm. Hg or over) drivers (53 deaths); (*c*) fathers of "normotensive" (B.P. under 160/95) drivers (121 deaths).

A similar analysis of the diastolic pressures of the siblings (both sexes) aged 45–60 of hypertensive subjects aged 45–60 in the series of Hamilton et al. (1954c) also shows two such overlapping distributions.

Thus we have shown that, in a population sample, an apparently continuous blood-pressure distribution curve may mask a bimodal distribution; and that this may be uncovered by means of the inheritance factor, by subdividing the sample according to ages at death of the parents. This reveals a special group of hypertensive subjects closely associated with premature death in one or both parents. Furthermore, we have obtained evidence that in this population the rise in mean pressures between 45 and 60 years is due to the increasing numbers of hypertensives in the sample as age advances. All these findings corroborate the hypothesis that high blood-pressure without evident cause is a specific disease with single-gene inheritance.

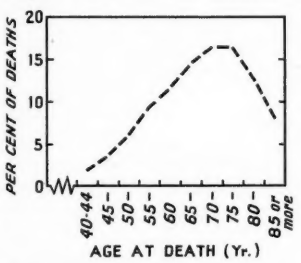


Fig. 6—Distribution of ages at death in all men in England and Wales, 1957. Percentage of deaths from all causes in each age-group, deaths under 40 years excluded (Registrar General 1958).

OCCUPATIONAL DIFFERENCES

Among the 302 busmen aged 45–60 for whom we have full data on the length of life of parents, the prevalence of hypertension in the conductors is 18%, and in the drivers half as much again—27%. (We have taken 160 mm. Hg systolic and 95 mm. diastolic to be the lower limit of "hypertension", as recommended by an Expert Committee of the World Health Organisation [1959].) The length of life of the parents of all drivers and conductors is compared in table I, which shows that there is little difference between the two occupations in the proportions losing a parent from death in middle age (49% and 52%). It appears, therefore, that if length of life of parents can be accepted as a rough measure of genetic "loading" for hypertension, while drivers and conductors have similar inheritance their prevalence of hypertension is different.

When the men are classified according to the length of life of parents, the prevalence of hypertension in drivers whose parents died in middle age is 34%, but in conductors it is only 18% (table II). Among busmen whose parents lived to old age, however, the prevalence of hypertension was similar in the two occupations—20% and 18% (table II). This is apparent from the distribution curves already given. Thus if the trough between the two peaks of fig. 1*b* and fig. 2*b* is accepted as the division between normotensives and hypertensives, drivers whose parents died in middle age show a higher proportion of hypertensives (second peak of fig. 1*b*) than do conductors (second peak of fig. 2*b*). The curves of systolic pressures of men whose parents lived to old age, again, are fairly similar for drivers (fig. 1*c*) and conductors (fig. 2*c*). Thus almost the whole of the difference in hypertension between drivers and conductors is in the men with a parent dying in middle age.

TABLE I—LENGTH OF LIFE OF PARENTS OF BUSMEN AGED 45–60

Length of life of parents	Drivers	Conductors
Mother died in middle age ..	19	18
Father ,, ,, ..	24 } 49%	27 } 52%
Both parents died in ,, ..	6	7
Both parents lived to old age ..	51%	48%
	n=186, 100%	n=116, 100%

Middle age=40–64 years. Old age=65 years and over.
n=total number of men.

FATHERS OF BUSMEN

Another test of the hypothesis will now be described. Do the *fathers* of hypertensive busmen segregate into normotensives and hypertensives, showing a bimodal distribution of blood-pressures, in contrast to the fathers of

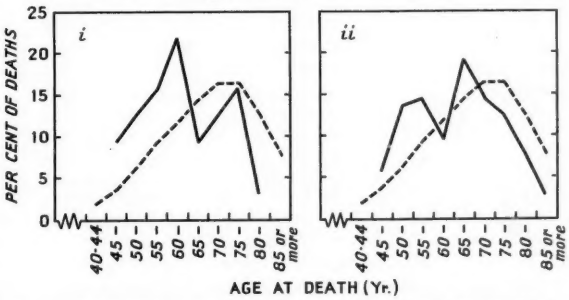


Fig. 8—Distribution of ages at death in fathers of male hypertensives (percentage of deaths from all causes in each age-group, deaths under 40 years excluded): (*i*) fathers of male "essential hypertensives" (Platt 1947) (32 deaths); (*ii*) fathers of male "essential hypertensives" and men with "nephrosclerosis" (Sobye 1948) (104 deaths).

TABLE II—BLOOD-PRESSURE OF BUSMEN AGED 45–60 ACCORDING TO LENGTH OF LIFE OF PARENTS

Length of life of parents	Occupation	No.	No. and proportion hypertensive
One or both died in middle age	Drivers	90	31 (*34%*•)
	Conductors	60	11 (*18%*•)
Both lived to old age	Drivers	96	19 (*20%*)
	Conductors	56	10 (*18%*)

• Difference significant, $p<0.05$.
Hypertensive = casual B.P. of 160/95 or above.

men having lower pressures? Again we must use data on ages at death since we have no information about the fathers' blood-pressures. Busmen are once more divided into hypertensives and normotensives at the pressure level of 160 systolic and 95 diastolic (World Health Organisation 1959)—figs. 1*b* and 5*bb* suggest that these figures represent a real break, at least in busmen—and the test is to see whether in fact the distribution of ages at death of the fathers of hypertensive sons is bimodal and fathers of normotensive sons unimodal.

Fathers of Drivers

Fig. 6 illustrates the distribution of all male deaths in England and Wales in 1957 at ages of 40 and over (Registrar General 1958): 2% of the deaths occurred at 40–44 years, 3·5% at 45–49 years, and so on. The shape of this curve was essentially the same in London and in 1947 and 1937.

Fig. 7 shows the distribution of ages at death of the fathers of the bus drivers. Fig. 7*a*, fathers of all drivers, is similar to fig. 6 for all men in the country. Fig. 7*b*, fathers of hypertensive drivers (160/95 and above), is a bimodal distribution; fig. 7*c*, fathers of normotensive drivers (under 160/95), is similar again to fig. 6. The fathers of hypertensives (fig. 7*b*) have segregated remarkably clearly into two groups, with an early peak of mortality about 60 years of age (where it might be expected if due to hypertension and arterial disease) as well as the usual one in the early seventies.

Published data giving the age at death of the fathers of hypertensives are available from two recent sources—Platt (1947) and Sobye (1948). In Platt's series propositi having hypertension without evident cause can readily be identified. Sobye's propositi comprise such cases, and also men with "nephrosclerosis" which seems to correspond to malignant essential hypertension. Fig. 8 (*i*) and (*ii*) show the distribution of the ages at death of the fathers of male propositi in these series. As in fig. 7*b*, there is a clear indication of two peaks in each of them. Thus, the distributions of ages at death of the fathers of the three groups of hypertensives are all apparently bimodal, in contrast to the distribution of the fathers of normotensives (fig. 7*c*).

Numbers of hypertensive *conductors* are too small to allow similar analysis.

The *mothers* of busmen do not show such clear differences. There are more deaths in middle age among the mothers of sons with high blood-pressure than with low; but numbers are too small for detailed analysis.

Discussion

The very simple figures presented here relate to exceedingly difficult questions.

However it arises, high blood-pressure is a "disease" in any ordinary sense of the term since it lowers the expectation of life. The question is, first, whether high blood-pressure occurring as an isolated phenomenon is a disease entity or merely represents the tail end of a continuous and graded distribution; and, secondly, what are the causes of it. Heredity obviously is a major cause. Is transmission by a dominant gene of almost complete manifestation, or is inheritance—like height and intelligence—by multiple genes? Does everyone inherit a level of blood-pressure, which in some is high (McKusick 1959); or do some inherit a specific disease, essential hypertension? Manifestly, further study will be on a surer basis if the search is focused on the cause or causes of a specific disease, whose victims are qualitatively different from the rest of the population. Moreover, the possibilities of prevention may be greater if hypertension is ascribable to some particular chemical, hormonal, or enzymatic anomaly which may be corrected, rather than to the unfortunate end of a universal distribution involving multiple causes.

"Continuous" and Bimodal Distributions

In our introduction we described how "continuity" and the apparent absence of bimodality in the distribution of blood-pressures formed the basis of Pickering's hypothesis. Discussing these distributions, Hamilton et al. (1954a) noted that "frequencies of measured blood pressures depart rather seriously from the normal form, one obvious departure being positive skewness [a longer tail to the right] which is evident at all ages". It is known, however, that curves of this kind can in fact conceal more than one quite distinct distribution. In a full discussion of a genetic problem involving this same question, Harris and Smith (1949) showed how the combination of two populations can produce either a bimodal or a unimodal continuous distribution. The factors concerned are the relative sizes of the two populations, the size of the difference between their means, and the size of the standard deviations (or scatter of observations) in the two populations. If one of the populations is much smaller than the other, bimodality is unlikely to appear even with a comparatively large separation of the means; similarly, two peaks will not be seen if the means of the two populations are close, even though both populations are of about the same size. This last point is illustrated by the "continuous" diastolic curve of fig. 5*b*. Fig. 5*bb* shows that this curve represents the combination of two nearly equal-sized populations, the mean values of which are too close to permit appearance of bimodality in the combined curve.

In population samples such as those of Hamilton et al. (1954a) or of Miall and Oldham (1955), and in the bus drivers and conductors reported here, there are probably two reasons why systolic curves show only one peak. First, the hypertensive population is only about a quarter of the size of the normotensive; hence, in accordance with Harris and Smith (1949), bimodality may not be obvious. Second, and perhaps more important, cross-sectional studies such as the present must include some who are in the process of developing hypertension and whose pressures therefore will lie between those of normotensives and hypertensives: these will tend to blur bimodality. This interpretation is borne out by the classification of drivers according to the length of life of their parents (fig. 1). We were able to demonstrate a bimodal distribution in one group (fig. 1*b*), and an apparently continuous curve in the other (fig. 1*c*). But this continuous curve had a peak lying between those of the two peaks in fig. 1*b*, and it may be that this fig. 1*c* includes not only men with normal pressure and men with high pressure but a goodly number also of men

developing high pressure. This point will be clearer when a full analysis of the experience at 60–65 years of age can be made. Meanwhile, it looks as if the " continuous " distribution of systolic pressures of all drivers (fig. 1*a*) may represent the combination of three populations—normotensives (the left peak of fig. 1*b*), hypertensives (the right peak of fig. 1*b*), and an intermediate or mixed group (fig. 1*c*) which is obscuring the contrast between the other two.

There is another side to this question. Any population sample of men in middle age consists of the survivors of an original and larger " cohort ". A reasonable assumption might be that by middle age 5% of this cohort will be missing because of hypertension. The chance of demonstrating bimodality in middle-aged population samples is thereby lessened. For instance, the distribution of drivers in fig. 1*a* would show a clearer picture of two peaks if 5% of hypertensives were added, and with 10% of hypertensives bimodality would be striking. These problems of defining who is being studied are crucial in a chronic and lethal disease such as hypertension. In epidemiological surveys it is necessary always to ask: (1) Who is present? (2) How did they get there? (3) Who got away? " Selection in " is a well-recognised source of bias in dealing with hospital patients or other special groups; but " selection out " is particularly important, and often exceedingly difficult to evaluate, in any group taken to represent the general population (Morris 1957).

Rise of Mean Pressures with Age

Our data on drivers corroborate the hypothesis that the average increase of blood-pressure in population groups during middle age is due to the increasing numbers of individuals with hypertension and not to a general and physiological rise of pressure. The suggestion is that the change in fig. 3*a* from the curve of 45–54 years to that of 55–60 is complicated and dynamic, involving several different population movements. However, static cross-sectional studies such as ours can only provide pointers to what may be happening as men pass through middle age. The only satisfactory answer to this question lies in prospective study, actually following large numbers of individuals. But if the rise of mean pressures of population groups with age can be explained even tentatively by the emergence of a greater proportion of individuals with a specific disease, the use of age-adjusted scores to estimate the resemblance between the pressures of first degree relatives (Hamilton et al. 1954c, Miall and Oldham 1955, Fraser Roberts 1958) is not valid. In fact these " scores " seem to have smoothed out existing bimodality.

Blood-pressure Differences Between Drivers and Conductors

Pickering and his colleagues (Hamilton et al. 1954c) and Smirk (1957) emphasise that environmental factors may strongly affect habitual blood-pressure levels. The main source of information about such factors in the near future is likely to be geographical pathology; for example, the high salt content of drinking-water in the Bahamas has been related to the high prevalence of hypertension there (Kohlstaedt et al. 1958). There are many such experiments of opportunity awaiting study (World Health Organisation 1959). Obstetric studies may yield important clues in this country (Gibson and Platt 1959); furthermore, two studies have suggested that the prevalence of hypertension may vary according to the physical activity of work (Morris and Crawford 1958, Kagan 1959).

The suggestion that drivers and conductors have a similar start in terms of genetic " loading " (table I) but respond differently (the conductors showing less hypertension than the drivers) raises questions about the effect of environment. But even if this finding is confirmed, it cannot be assumed that an environmental factor is responsible; or if it is, that the factor is physical activity of work. Choice of job is not random. Thus, differences in physique are brought with them by drivers and conductors into the job (Morris, Heady, and Raffle 1956) and there may be hereditary factors in this. Such factors could be related to blood-pressure levels without closely affecting mortality from hypertension. Levels in recruits have not yet been studied; and we are also now examining the distribution of blood-pressures in relation to skinfolds, arm circumference, &c., within the two occupations. The evidence that physical activity/inactivity produces occupational differences in hypertension is slight compared with that on coronary-artery heart-disease (Morris and Crawford 1958). The possibility that emotional strains, for example, and disturbances of other homœostatic mechanisms (Page and Corcoran 1952) are responsible for the difference in blood-pressure levels between drivers and conductors has not yet been examined. In general we have here an illustration of what is becoming a most interesting field for research in social medicine: men with different backgrounds select different jobs, which mean living in different environments. It is becoming possible to make some systematic study of the processes involved.

Mortality of Fathers

Age at death can be only a very crude indication of the presence or absence of hypertension. In spite of this, the distribution of deaths in fathers of hypertensive drivers shows a clear division into two groups, in clear contrast to that in fathers of normotensive drivers (fig. 7). If this finding is confirmed, it suggests that hypertension may be even more lethal than is presently believed. It is conceivable that the analysis of fathers' age at death is indicating the action of a gene or genes producing hypertension and, in association with arterial disease, perhaps even more generally, profoundly affecting length of life. (The contribution of hypertension to the hereditary component of coronary-artery heart-disease certainly needs to be re-examined.) Levy et al. (1944) have shown that young men with " transient hypertension " not only have higher death-rates in later life from cardiovascular disease than normotensives but also significantly higher death-rates from all other causes. More generally, the demonstration by two complementary methods of a close association between premature death of parents and the single casual blood-pressure reading in sons suggests that a casual pressure may mean more, at any rate in middle age and under the circumstances of the present study, than is commonly supposed. Further studies, which must also attempt to get accurate data on the causes of death of parents, are essential.

Identification of a Syndrome

We have shown that among middle-aged bus drivers having high blood-pressure without evident cause, the majority form a discreet group when classified according to the length of life of their parents. Numbers in this group rise sharply in late middle age. A syndrome can thus be identified epidemiologically (Morris 1957) corresponding to the common notion of " essential hypertension ". Biochemical and genetic studies may eventually settle these questions by discovering the postulated *qualitative* difference between hypertensive and normo-

tensive individuals. There is certainly every reason to seek it. The same classification of bus conductors reveals fewer men with the " syndrome "—which suggests that environmental factors may be concerned in its production. The evidence of the clustering of this syndrome in families may indicate clinical possibilities for prevention.

There are other men having high blood-pressure, cause at present unknown. Some of these may be merely at the tail end of a " normal " distribution in the general population. Others may represent other syndromes that await definition.

Summary and Conclusions

As part of a clinical survey focused on cardiovascular disease, casual blood-pressures have been taken on a sample of 302 London busmen aged 45–60 and questions asked about their parents' length of life.

Systolic pressures of bus drivers, on plotting, were distributed " continuously " with a longish tail to the right. When the men were classified in terms of the length of life of their parents it was apparent that this curve combined and concealed more than one frequency distribution. About half the drivers—those whose parents lived to old age (65 or over)—showed a roughly normal distribution of systolic pressure with a peak about 150 mm. Hg. In contrast, among the other half of the drivers—those with a parent dead in middle age (40–64) —the distribution was bimodal: the men divided into two fairly equal groups with a first peak about 140 mm. Hg and a second hypertensive peak about 175.

The average systolic pressure among all drivers *rose with age* from 147 at 45–54 years to 158 at 55–60. However, when parents had lived to old age, systolic pressures in the drivers of 55–60 showed almost the same distribution as in the drivers of 45–54; the average pressure in these men did not rise significantly with age. Among men with a parent dead in middle age the bimodal distribution of blood-pressures showed two distinct trends. Numbers in the first peak fell between ages 45–54 and ages 55–60; but the numbers forming the second hypertensive peak rose sharply at 55–60, so much so that the average level for all drivers aged 55–60 was raised above that of all aged 45–54. The average rise of pressure during middle age in drivers seems to be due not to any general or physiological rise in levels but to a fraction of the men, to the emergence of a minority of individuals from particular families with high blood-pressure.

Diastolic pressures were distributed " continuously " in drivers whose parents lived to old age—and also in the group of men with a parent dead in middle age. But further classification of this latter group by their systolic pressures, into those below and above 160 mm. Hg, showed that this curve of diastolic pressures was in fact made up of two overlapping but quite distinct distributions, with one peak at 85 and a second (hypertensive) peak at 100 mm. Hg.

The proportion of *drivers* with parents dead in middle age was about the same as the proportion of *conductors*; but there were substantially more drivers with high blood-pressure than conductors. This was mainly because in the men with a parent dead in middle age more drivers than conductors were hypertensive; the second hypertensive peak was smaller in the conductors and there was no significant rise of pressures with age in them. These advantages may be the effect of environment.

Analysis of these casual readings by family history and the trends with age and occupation suggest that the majority of busmen having high blood-pressure without evident cause belong to a characteristic group—those forming the hypertensive peak disclosed by these analyses. By *epidemiological* methods a *syndrome* has thus been identified which corresponds to the common clinical notion of " essential hypertension "; and this supports the hypothesis that essential hypertension is a specific disease entity. The condition appears to cluster remarkably in families and to be strongly hereditary, possibly transmitted by a dominant gene shown here to associate premature death of parents with hypertension in sons. Such hypertension may, however, be modifiable by environment: it seems to have multiple causes. There is every reason to continue the search for methods—clinical and biochemical—of identifying individuals with this syndrome.

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REFERENCES

Bechgaard, P., Kopp, H., Nielsen, J. (1956) *Acta med. scand.* **154**, suppl. 312.
Bøe, J., Humerfelt, S., Wedervang, F. (1957) *ibid.* **157**, suppl. 321.
Fishberg, A. M. (1954) Hypertension and Nephritis. London.
Gibson, G. B., Platt, R. (1959) *Brit. med. J.* ii, 159.
Hamilton, M., Pickering, G. W., Roberts, J. A. F., Sowry, G. S. C. (1954a) *Clin. Sci.* **13**, 11.
— — — — (1954b) *ibid.* p. 37.
— — — — (1954c) *ibid.* p. 273.
Harris, H., Smith, C. A. B. (1949) *Ann. Eugen.* **14**, 309.
Kagan, A. R. (1959) Unpublished.
Kohlstaedt, K. G., Moser, M., Francis, T., Neel, J., Moore, F. (1958) *Circulation* **17**, 728.
Levy, R. L., Hillman, C. C., Stroud, W. D., White, P. D. (1944) *J. Amer. med. Ass.* **126**, 829.
Master, A. M., Dublin, L. I., Marks, H. H. (1950) *ibid.* **143**, 1464.
McKusick, V. A. (1959) *Mod. Conc. Cardiov. Dis.* **28**, 535.
Miall, W. E., Oldham, P. D. (1955) *Clin. Sci.* **14**, 459.
Morris, J. N. (1957) Uses of Epidemiology. Edinburgh.
— Crawford, M. D. (1958) *Brit. med. J.* ii, 1485.
— Heady, J. A., Raffle, P. A. B. (1956) *Lancet*, ii, 569.
Page, I. H., Corcoran, A. C. (1952) *Circulation*, **6**, 286.
Pickering, G. W. (1955) High Blood Pressure. London.
Platt, R. (1947) *Quart. J. Med.* **16**, 111.
— (1959) *Lancet*, ii, 55.
Registrar General (1958) Statistical Review of England and Wales, 1957. Part I. Tables, Medical. H.M. Stationery Office.
Roberts, J. A. F. (1958) *in* Toxæmic Hypertension in Pregnancy (edited by N. F. Morris and J. C. McClure Browne); p. 4. London.
Robinson, S. C., Brucer, M. (1939) *Arch. intern. Med.* **64**, 409.
Smirk, F. H. (1957) High Arterial Pressure. Oxford.
Sobye, P. (1948) Heredity in Essential Hypertension and Nephrosclerosis. Copenhagen.
Weitz, W. (1942) *Dtsch. med. Wschr.* **68**, 105.
World Health Organisation (1959) First Report of the Expert Committee on Cardiovascular Diseases and Hypertension. *Tech. Rep. Ser. Wld Hlth Org.* no. 168.

" . . . Ideas have many of the properties which we find in genes . . . But . . . the processes of transmission are different. Ideas and knowledge are not restricted in transmission from parent to offspring. They can spread sideways as well as vertically down the generations, can spread outside the limits of the family—indeed, beyond any biological relationship—and they can do so with a speed impossible to genes. . . . The communication of ideas . . . can also be used to suppress or erase hereditary differences, as for example where medicine succeeds in removing the menace of a hereditary disorder or education smooths out the individual idiosyncrasies of those who are taught. It can lead us to confuse knowledge, which is social and rapidly increasing, with ability, which is genetical and rising, so far as we can see, not at all. It can blind us to the genetical consequences of our social changes—consequences which are none the less important because they are slow and obscure. This interplay of the social and the hereditary has only just been recognised, let alone studied. Yet study it—and study it deeply—we must, if we are to come to any true understanding of what makes man what he is."—Prof. KENNETH MATHER, *The Listener*, Oct. 8, 1959, p. 567.

HERPETIC WHITLOW
A FORM OF CROSS-INFECTION IN HOSPITALS

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SOON after the establishment of the septic hand clinic at this hospital a relatively high incidence of septic lesions of the fingers was noted amongst nursing staff, most of the cases occurring in the neurosurgical unit. Altogether 54 cases have been observed with an average of three weeks' loss of work per case. There is reason to believe that the condition is a hitherto unrecognised clinical entity which is a form of hospital cross-infection and is probably common.

Clinical Picture

All the lesions occurred in nurses and affected the digits, the thumb or index finger being most often involved. In only 5 of the 54 cases was more than one digit infected. The distribution of the lesions is shown in fig. 1.

The whitlow starts suddenly as an area of irritation which soon becomes very painful. It first appears as a deep vesicle, generally on the terminal segment of the digit, usually near the nail. Soon other vesicles appear. Such early lesions are seldom observed by the clinician: an example is illustrated in fig. 2*a*. The vesicles coalesce, giving rise to a honeycombed appearance (fig. 2*b*), and may remain localised (fig. 2*c*), or, more usually, spread by crops of fresh vesicles (fig. 2*d*). These eventually also coalesce, leading to much superficial tissue destruction. Spread often occurs around the nail and the tip of the finger, but may also involve the more proximal parts of the finger. Occasionally a group of vesicles coalesce to form a large subcuticular blister (fig. 2*e*). The process commonly extends under the nail, which becomes separated wholly or partly from its underlying matrix.

At a later stage the appearance suggests a whitlow with pus under the cuticle (fig. 2*f*). When the whitlow is incised, however, there is no pus. In the earlier phases it contains only a little clear fluid, which later becomes turbid; and still later thick yellow necrotic debris adherent to the underlying true dermis is found. In almost all cases the tell-tale small deep vesicles beyond the edge of the lesion make clinical diagnosis possible.

Fever and constitutional disturbance are uncommon. In 7 patients there was slight elevation of temperature, and in 13 there was transient enlargement of the axillary glands. Pain, however, is often severe, the affected finger throbbing and being tender to a degree that in a bacterial pulp infection would demand immediate incision. The subcutaneous tissues are unaffected, and, although the pulp is often tender, there is little or no increased tension in it.

The severity of the individual cases varies considerably, but all lesions pursue a similar course. There is a tendency for them to spread for about ten days, during which the pain continues unabated. After ten days, objective symptoms improve suddenly and the vesicles begin to dry and form a crust. The change from a painful, angry-looking finger to a painless and obviously resolving one is often dramatic. After a further seven days the crusts begin to separate, leaving healthy skin and a normal finger underneath. If the nail has been undermined, it becomes dry and is shed later as the new nail grows beneath it.

The natural history of the lesion thus occupies two and a half to three weeks. If the lesion is incised, secondary infection occurs and this prolongs the period of disability. Such a lesion often yields a profuse growth of *Staphylococcus pyogenes*, usually either of the same phage type as in the patient's nose, or of the prevalent "hospital type". The lesions can thus be readily mistaken for staphylococcal pyoderma or ordinary subcuticular whitlow.

From the clinical point of view a notable feature of the condition is its complete resistance to all forms of treatment. The antiseptics and antibiotics in common use are of no value, even if the staphylococci isolated are sensitive to the drug. Experience has shown that the best management is strict non-interference, treatment being limited to the application of a dry dressing locally for protection and the prescription of analgesics for the pain. On a few occasions only has the extent and tension of the raised cuticle called for incision, and then simple incision without removing the cuticle has proved effective.

Most cases were followed up for only a relatively short time after the initial lesions, but even so in 7 cases there was a recurrence at the original site. The recurrences were similar to, but milder than, the original attacks, and occurred from one month to three years later. One nurse whom we observed only at the time of a recurrence had had the initial lesion ten years previously, having been bitten by a child with herpetic stomatitis. In 2 cases more than one relapse occurred.

Despite careful inquiry, in most cases no history of trauma could be elicited. In 14 cases there was minor trauma; 5 patients gave a history of a cut, 5 of a scratch, and 2 of a pinprick, while in 2 there was a crack due to eczema. Nurses often injure their fingers, and the importance of a history of minor trauma is doubtful.

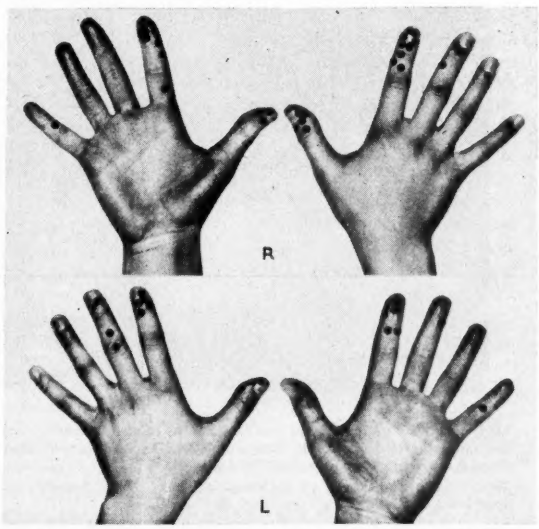

Fig. 1—Distribution of lesions in 50 cases of herpetic whitlow.

Laboratory Investigations

Bacteriology

It was assumed at first that the lesions were staphylococcal, and bacteriological tests were not carried out. Later, swabs were sent to the laboratory from a small number of cases after incision and these yielded *Staph. pyogenes* in some, while in others organisms were isolated which manifestly were not the cause of the lesions (e.g., coliform bacilli and *Streptococcus viridans*). More significantly, in a further group the cultures were sterile, and when this occurred in cases which were not on antibiotic treatment, a viral cause seemed most probable.

Virus Isolation

Material for virus isolation was obtained by puncturing an intact vesicle and drawing some of the fluid into a sterile capillary pipette. In every case the material was inoculated immediately into three tubes of primary human-amnion-cell monolayers maintained in Earle's solution containing 0·5% lactalbumin hydrolysate and 5% horse-serum. The tubes were then incubated in a stationary position at 37°C. Specimens of saliva and suction material were thoroughly mixed with 1 ml. of Hanks' saline containing antibiotics and kept at room temperature for one hour, and then centrifuged at 2000 r.p.m. for ten minutes. 0·1 ml. was then inoculated into each of two amnion tubes and incubated as above. In the case of material from vesicles a cytopathogenic effect characteristic of *Herpes simplex* virus was usually complete within twenty-four hours. Saliva and suction material often required up to three days for the degeneration to become obvious. Identification

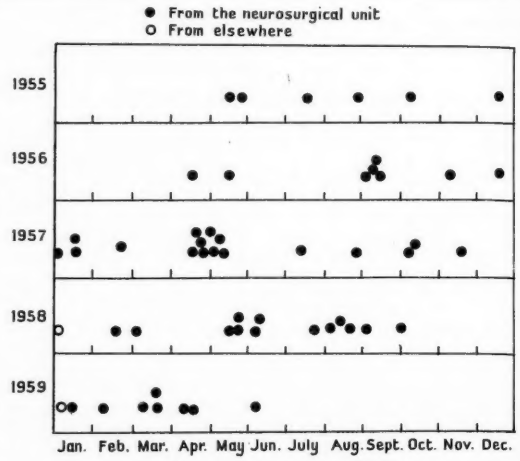

Fig. 3—Incidence of cases, 1955–59.

Fig. 2—Appearances of herpetic whitlow.

***a*, early lesion involving dorsal and lateral side of the nailbed. Note the characteristic outlying vesicle marked by the arrow. The lesions are seldom seen at this early stage.**

***b*, lesion involving most of terminal phalanx, with honeycomb appearance and yellowish material looking like pus.**

***c*, appearances typical of subcuticular whitlow. The island apparently containing pus is filled with yellow necrotic material.**

***d*, earlier lesion illustrating spread by means of crops of vesicles.**

***e*, large bullous lesion formed by the coalescence of vesicles. This form was infrequent.**

***f*, herpetic whitlow simulating the typical appearance of paronychia. Cases at this stage are often regarded and treated as staphylococcal lesions.**

VIROLOGICAL INVESTIGATIONS IN 14 CASES OF WHITLOW

Case no.	Virus isolation	Titre of neutralising antibodies to *Herpes simplex*	
		Prior to lesion	After lesion
1	No specimen	<8	32
2	+	<8	32
3	+	<8	32
4	+	<8	32
5	+	N.D.	32
6*	+	32	N.D.
7	+	<8	32
8	+	<8	64
9	+	<8	16
10	+	<8	32
11	+	<8	32
12	+	<8	16
13	+	<8	16
14*	+	32	N.D.

*=recurrence. N.D.=not done

was then carried out by neutralisation with high-titre herpes antisera prepared in rabbits.

Serology

Antibody levels were determined by neutralisation tests in amnion-cell cultures. Sera were inactivated at 56°C for thirty minutes, and serial dilutions were made in Hanks' solution. 0·3 ml. of each dilution was mixed with an equal volume of *Herpes simplex* virus suspension diluted to contain 100 TCD_{50} of virus per 0·1 ml. The mixtures were kept at 37°C for one hour, and 0·2 ml. volumes from each tube were then inoculated into duplicate amnion tubes and incubated at 37°C. Results were read when the control virus tubes showed 4+ degeneration—usually within three to four days. The antibody end-point was expressed as the reciprocal of the highest initial dilution of serum producing 1+ or less degeneration.

Results

Virus studies were initiated in June, 1958. Of the 14 cases observed since then *Herpes simplex* virus was isolated from 13. From the same date a sample of blood was taken from all nurses starting work in the neurosurgical wards; and from those in whom lesions developed a second specimen of blood was obtained about two weeks after the onset of infection. It was thus possible to compare the levels of neutralising antibodies before and after a lesion. The results are summarised in the accompanying table. In all but 2 cases no antibody could be detected before the appearance of a lesion. These were therefore primary infections. In the 2 cases in which antibodies were present at the onset, there was a clear history of a preceding infection at the same site. These were therefore herpetic recurrences.

Epidemiology

The incidence of cases is shown in fig. 3. This reveals a number of small outbreaks suggesting that several cases had become infected from a single source. In an effort to trace the source of infection a sample of saliva was obtained from every patient on admission. Herpes virus was isolated from 4 (1·2%) of 328 patients. These 4 were salivary carriers, since none of them showed clinical evidence of herpes infection. This incidence proved to be too low to account for the number of lesions observed.

Inquiry about herpetic lesions in the wards revealed that after brain operations, and in particular after the removal of acoustic neuromata, herpetic eruptions of the face were not uncommon. However, it was found that only 1 case of whitlow had its source in these clinically obvious lesions. Presumably in these instances adequate precautions against transmission of infection were taken.

In the wards under investigation tracheotomy was often carried out after cranial surgery, in order to prevent accumulation of bronchial secretions in the unconscious patient. These secretions were usually removed by suction through the mouth when possible, or through the tracheotomy tube. Suction was carried out by means of a rubber catheter linked to an electrical suction pump through a Wolff bottle containing an antiseptic. The catheter itself, however, was manipulated by the bare hand of the nurse, and several nurses might attend the same patient. The bronchial secretions of these patients were examined by taking a swab from the catheter after withdrawal. Out of 63 cases examined *Herpes simplex* virus was isolated from 4 (6·5%). Though the numbers are relatively small, this is a significantly higher rate than in preoperative patients ($p < 0.01$). In none of these 4 cases was there any clinical evidence of herpes infection. The last 6 cases of herpetic whitlow observed were indisputably traced to the handling of the catheters used on these 4 patients.

The immune state of the nursing population at risk was also investigated. During one year blood samples from all the nurses starting work in the neurosurgical unit were examined. The sera of 149 nurses were tested at a dilution of 1 in 8 for neutralising antibodies against herpes virus. 73 nurses (49%) were without antibodies and therefore could be regarded as the population at risk. Of these, 12 (16·5%) developed lesions. Almost all the nursing staff were within the age-group 18–29 and came from homes of good socioeconomic level.

51 of the nurses who had no antibodies when beginning work could be followed up, and were re-examined after six months or longer on ward duty. Apart from the 12 in whom finger infections developed, none acquired antibodies. Subclinical infections amongst this group of nurses therefore did not occur.

2 volunteers who had neutralising antibodies and suffered from recurrent herpetic eruptions were challenged with 1000 TCD_{50} of herpes virus recently isolated and passed only once through primary amnion cells. The virus was inoculated both by intradermal injection and by scarification. No vesicular lesions were obtained, only an allergic response of erythema and induration, suggesting that infection occurs only in the absence of antibodies.

Prevention

Upper-respiratory secretions in patients with post-operative or other forms of respiratory infection should in general be regarded as potentially infectious. When such secretions containing herpes virus have to be handled, no ill effects will follow provided the person has immunity. It is the particular concatenation of circumstances in which non-immune young people are called upon to handle such infectious material that leads to herpetic whitlow. In practice, the nature and the source of the contagion being known, it proved a simple matter to avoid infection. The wearing of rubber gloves whenever suction was required proved a safeguard. In cases of extreme emergency if bare hands have to be used, their subsequent immersion for several minutes in 1:1000 cetrimide might possibly be of value.

Discussion

Whitlow appears to be a hitherto unrecognised form of herpetic infection. Apart from *Herpes simplex* infections associated with eczema, primary infections of the skin have rarely been described. There is a single reference to infection of the unbroken skin (Scott et al. 1952), the other cases following trauma such as a bite, burn, or cut (Findlay and MacCallum 1940, Scott et al. 1952, Dud-

geon 1954, Scott 1957). All the cases reported have been associated with regional adenitis, constitutional disturbance, and a clinically obvious source of herpes, such as stomatitis or cold sore in a contact. During a ward outbreak of Kaposi's eruption among children Pugh et al. (1955) observed vesicular eruptions of the hands and forearms in 2 nurses but they described no details.

Herpetic whitlow differs strikingly from all these. It is not associated with trauma, fever and adenitis are usually absent, and there is generally no obvious source of herpes. Moreover, it is probably far from rare in hospitals. Most of the cases are presumably mistaken for staphylococcal septic lesions, the error being supported by the isolation of *Staph. pyogenes*, so commonly present on the fingers.

Two possible sources of herpes virus were found: patients with obvious herpetic lesions, and symptomless salivary carriers. It is well known that recurrent herpetic eruptions often follow brain operations and section of the trigeminal sensory root (Carton and Kilbourne 1952, Behrman and Knight 1954, Knight 1957). Except for a single case, however, this source could not be incriminated.

The salivary carrier-rate amongst the patients on admission was comparable with that found by Buddingh et al. (1953) in a similar age-group. The number of such carriers was too low, however, to account for the frequency of finger infections, and in any case these patients received no mouth toilet from the nurses. Salivary carrier-rates are known to be much higher in children and might cause herpetic whitlows in those handling them.

Fever is a recognised cause of recurrent clinical herpes. Even artificially induced fever may produce herpetic recurrence in 46% of patients (Carpenter et al. 1940). After brain operations, upper respiratory infections with fever are common. We were able to show that among such patients there is also a significant increase in the proportion of symptomless carriers. These were the cases responsible for the soiling of the nurses' hands with infectious material.

There is experimental evidence that it is difficult to produce primary staphylococcal lesions of the skin (Elek and Conen 1957). The discovery of a type of whitlow caused by herpes virus suggests that certain lesions now regarded as primarily staphylococcal infections may in fact be viral in origin with secondary staphylococcal sepsis.

Summary

In nurses working in a neurosurgical unit a hitherto unrecognised form of finger infection, due to *Herpes simplex* virus, was found to be common.

The lesion can be readily mistaken for a staphylococcal infection, since it becomes secondarily infected with *Staphylococcus pyogenes*; but it is not associated with trauma, regional adenitis, or constitutional upset.

The source was traced to the respiratory secretions of patients: after operation, about 6% excreted *Herpes simplex* virus without any clinical evidence of infection.

49% of the nursing population was found to be susceptible.

Herpetic whitlow may be common in hospitals.

REFERENCES

Behrman, S., Knight, G. (1954) *Neurology*, **4**, 525.
Buddingh, G. J., Schrum, D. I., Lanier, J. C., Guidry, D. J. (1953) *Pediatrics*, **11**, 595.
Carpenter, C. M., Boak, R. A., Warren, S. L. (1940) *J. exp. Med.* **71**, 155.
Carton, C. A., Kilbourne, E. D. (1952) *New Engl. J. Med.* **246**, 172.
Dudgeon, J. A. (1954) *Med. Pr.* **232**, 546.
Elek, S. D., Conen, P. E. (1957) *Brit. J. exp. Path.* **38**, 573.
Findlay, G. M., MacCallum, F. O. (1940) *Lancet*, i, 259.
Knight, G. C. (1957) *Postgrad. med. J.* **33**, 448.
Pugh, R. C. B., Dudgeon, J. A., Bodian, M. J. (1955) *J. Path. Bact.* **69**, 67.
Scott, T. F. McN. (1957) *Amer. J. Ophthal.* **43**, 134.
— Corriell, L. L., Blank, H., Burgoon, C. F. (1952) *J. Pediat.* **41**, 835.

SURGICAL TREATMENT OF MITRAL STENOSIS
WITH PARTICULAR REFERENCE TO THE TRANSVENTRICULAR APPROACH WITH A MECHANICAL DILATOR

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IN the early experimental phase of surgical treatment for mitral stenosis opinion was divided on whether the best approach to the valve was transatrial or transventricular.

Lauder Brunton (1902), introducing the concept of valvulotomy, felt that the ventricle was less likely to bleed than the atrium. He advised that the knife should be introduced during diastole in order to avoid injury of the opposite ventricular wall.

Bernheim (1909) supported Brunton's view and in experimental work found it easy to divide a stenosing ligature by passing a cutting hook through the apex of the left ventricle.

Allen and Graham (1922) devised a cardioscope and, influenced by the difficulty of controlling bleeding from needle punctures of the atrium, at first passed their instrument through the wall of the left ventricle. This caused a considerable disturbance of the heart's action and led to arrest in diastole in more than half the animals. They concluded that the auricular appendage was the most suitable structure through which to pass the cardioscope.

Cutler and Levine (1923) operated on a girl of 12 with mitral stenosis. " It seemed wiser to use the simpler and more speedy route through the ventricular wall with the valvulotome in the first human case."

Allen (1924) again favoured the auricular approach because of easy access and because the auricle could be manipulated with little disturbance; and there was no mortality in the experimental animals.

Cutler et al. (1924) considered that there were several reasons against the auricular approach, including the risk of finding thrombus in the auricle and " the risk of a tear in the distended, thinned out auricle ". They regarded postoperative thrombosis and embolism, consequent upon intimal injury, as more likely with the slower flow of blood in the auricle. They preferred the ventricular route, because the thick ventricular walls were easier to approach and safer to repair.

In 1925 Souttar used the auricular route for digital exploration of the mitral valve in a woman of 38.

Murray (1950) reported eight survivors from operation for mitral stenosis with a cardiovalvulotome which was introduced through the ventricle. He considered that there was great danger of hæmorrhage from the enlarged left atrium.

In 1948 Bailey in Philadelphia, Harken in Boston, and Brock in London used Souttar's procedure of exploration through the auricle and rupture of the commissures by digital pressure. This procedure soon was widely practised. It was appreciated that the dilated and hypertrophied auricle in mitral stenosis was easier to handle and held sutures much better than the slender, thin-walled, normal auricle. When hæmorrhage from the auricle was hard to control it was because fibrosis and shrinkage left too little room for easy passage of the finger or because the atrial wall was accidentally torn in the course of over-vigorous attempts to rupture the commissures. Cutler's fear of encountering thrombus in the atrium and causing embolism was soon confirmed,

but the superiority of the atrial over the ventricular route was for some years unquestioned. For digital exploration of the mitral valve it has remained so.

Difficulties with the Atrial Approach

Even at postmortem examination with the left atrium widely open recognition of the mitral commissures by direct inspection is often difficult because the cusps form a continuous sheet. It is not surprising that at operation when the valve must be palpated through an atrial approach the commissures are frequently not recognisable with any accuracy. Fortunately digital valvulotomy, which is the operation most frequently performed, does not primarily require accurate localisation of the commissures. Their approximate situation is obvious and pressure near them or merely the thrusting of a finger through the stenosed orifice is enough to tear the valve at its weakest point, almost always one or other commissure. After the finger has been passed through the orifice further commissural division can be achieved only at the cost of traction on some part of the heart. This falls at least on the valve ring and sometimes on the great vessels, although traction on the great vessels can be reduced or prevented by counterpressure with the hand on the outer surface of the heart. Repeated or prolonged traction disturbs the heart's action and may even cause cardiac arrest.

We have described (Logan and Turner 1953, Turner and Fraser 1956) our early experience in the diagnosis and treatment of mitral stenosis. In the first 100 valvulotomies of the present series, although the description "the anterior commissure was divided as far as the valve ring" was often recorded, if any commissure was completely divided it was by accident because the shape and extent of the commissures was not appreciated with certainty. Towards the end of this period unexpectedly easy division of the commissures was achieved in a few cases and this revealed the long curve of the anterior commissure and its well-defined anterior termination. Afterwards more strenuous efforts were made to achieve similar results in more difficult cases and adverse effects of traction on the heart were therefore often observed.

Some form of knife, tentatively used in the first hundred, was used with increasing frequency in an attempt to divide the sclerotic ring so often found surrounding the valve orifice. In addition to the minor difficulty of controlling the atrial incision when both finger and knife pass through it and the sensory privation caused by the presence of the knife between the finger and the region of the commissure a knife has the great disadvantage that the incision is made exactly where the blade is directed and this is not necessarily at the commissure. Accurate knowledge of the position and direction of the commissure is a theoretical prerequisite for its use and this knowledge is often unavailable. Many surgeons have found difficulty in recognising the commissures, in placing the knife with precision because of the impossibility of simultaneous palpation, and in cutting the commissures. These difficulties are reflected in the number of knives invented and the continued search for other methods of cutting the commissures. In our series a transatrial knife has rarely made any useful contribution.

The Transventricular Approach

As a result of failures with the standard techniques, it was decided to approach the mitral valve from the ventricle and to guide the instrument into position by transatrial palpation. In December, 1953, a short-bladed tenotome, passed through the anterior ventricular wall, was first used for mitral valvulotomy. This overcame some of the difficulties related to the use of the knife. Whereas manipulation of the knife in the same atrial incision as the finger often caused some loss of blood, control of the separate atrial and ventricular incisions presented no difficulty. With a knife of standard pattern held in the left hand it was possible to cut the valve. The knife could readily be felt by the atrial finger during incision of the valve. But the defect common to all knives remained—that it cut where it was directed and therefore required precise localisation of the commissures. This was accepted as precluding its continued use.

In May, 1954, one of us had the good fortune to observe Dubost perform mitral valvulotomy using the transatrial dilator which he had introduced because of dissatisfaction with the finger-and-knife technique. It was intended to follow his technique and with this in view an expanding dilator was devised by Dr. Maxwell Brown, late of Edinburgh Royal Infirmary, who, besides being an anæsthetist, is a skilled engineer. This instrument was first used in a case in which digital valvulotomy had failed. The handle was found to be so shaped that the expanding head could not be directed into the mitral valve. Consequently the instrument had to be introduced through the anterior ventricular wall. The commissures were successfully divided. At first there was much doubt about the propriety of using the ventricular route when the transatrial alternative was so successful in Dubost's hands. This doubt was increased when in the 6th case in which the transventricular route was used death from hæmorrhage followed shortly after operation and the source was believed to be the ventricular wound. During the next year the ventricular route was used only sporadically. When Dubost's instrument finally became available it was used by the transatrial route in 19 cases but trouble from entanglement of the instrument in the chordæ tendineæ and the personal preference acquired for the transventricular route combined to establish the latter as the preferable approach.

The dilator first used had a maximum spread of 3·5 cm. This was frequently too small fully to open both commissures. 5 cm. was considered the ideal spread and this was provided by the instrument later designed by Mr. O. S. Tubbs for use in this technique.

Use of a Dilator

The use of the transventricular dilator requires an exposure of the left ventricle only slightly better than that usually given by thoracotomy for the transatrial operation, and this can be gained by carrying the parietal incision more anteriorly or at most by dividing the costal cartilage below the incision. Unless there is massive atrial clot or valvular calcification, exploration of the valve with the finger through the atrium is followed by a gentle attempt at digital valvulotomy. If this fails the ventricle is incised near the apex (fig. 1); the dilator is introduced and its head is accurately placed in the valve orifice under the guidance of the atrial finger (fig. 2). No attempt is made to ensure that the head opens in any specific relationship to the axis of the orifice of the valve because, so far as has been ascertained, this does not affect the natural tendency of the valve to split along the line of the commissures. The dilator is opened just far enough to overcome the resistance offered by the valve and then withdrawn so that its effect can be assessed digitally. This may be

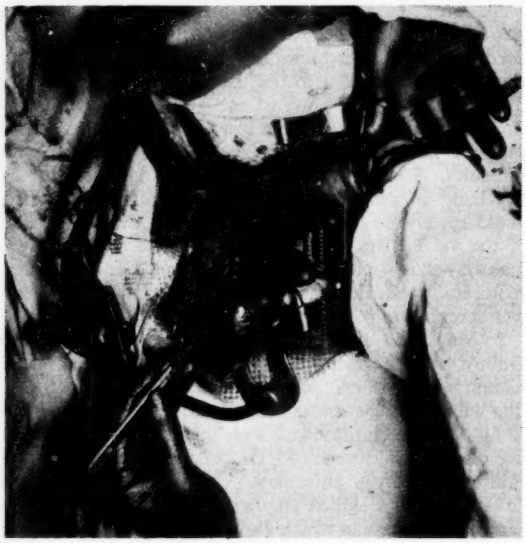

Fig. 1—Incision of ventricle. Right index is in the atrium. Left hand advances knife towards apex of left ventricle.

repeated several times but the use of the dilator must be abandoned if one commissure is completely divided while the other remains intact, or if neither gives way with the use of moderate force. If reflux is felt through the partly divided commissures it is probably better to pursue the attempt at complete valvulotomy provided that the reflux is judged to be the result of mere separation and not of other damage to cusps or chordæ. When the dilator is withdrawn bleeding from the ventricle is prevented by pressure with the thumb (fig. 3).

The transventricular dilator was first used on June 17, 1954. In the succeeding five years 537 mitral valvulotomies have been performed and the transventricular dilator has been used in 438 cases (81·5%). During the first of these years, although resort to the dilator was somewhat reluctant, it was used in 58 cases out of 110 (53%). By contrast, during the last year of this period it was used in 105 out of 113 cases (93%). Preliminary efforts at digital valvulotomy were never abandoned but became more and more gentle as satisfaction with the dilator technique increased, and it was appreciated that there was much less general disturbance to the heart.

Valvulotomy before and after the transventricular dilator came into use can be compared in the following respects: the technical advantages and disadvantages; the extent of commissural division; the incidence and severity of traumatic mitral incompetence; the incidence and cause of operative and early postoperative death. A comparison cannot yet be made of length of survival, duration of improvement, or need for reoperation, but there is some reason to believe that it will be favourable.

Advantages of a Dilator

Reluctance to subject the heart to the trauma of a difficult finger valvulotomy or to use a knife has gradually increased the proportion of cases in which the dilator is considered necessary.

In digital valvulotomy the finger does not recognise the commissure and then selectively tear the valve along it, but tears the valve and recognises the commissure by the site of the tear. The dilator shares with the finger the advantage that it divides the weakest parts of the stenosed valve and these are nearly always the adherent commissures.

The dilator provides its own counter-pressure so that at no time during its use is there dragging on the heart.

Greater and more controlled force can be applied to the valve with the dilator than with the finger. The dilator is as competent to divide the posterior as the anterior commissure while the finger and knife usually have difficulty with the posterior commissure which may require a " backhand " stroke when the operator works from the patient's left.

The principal disadvantage of the dilator is its tendency to open suddenly to its full extent when the force applied to it is not well controlled. This may result in tearing or partial detachment of a cusp. Mechanical stops in the dilator can be employed to prevent this but control can best be acquired by practice. In our unit the 5 cm. dilator is rarely used as the first instrument. A 3·5 cm.

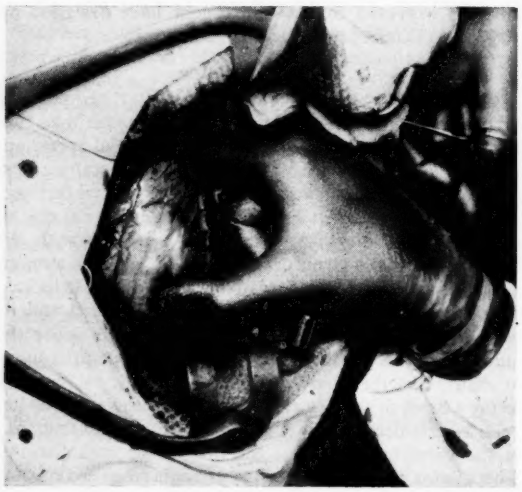

Fig. 2—Control of ventricular incision by thumb pressure while right index remains in the atrium.

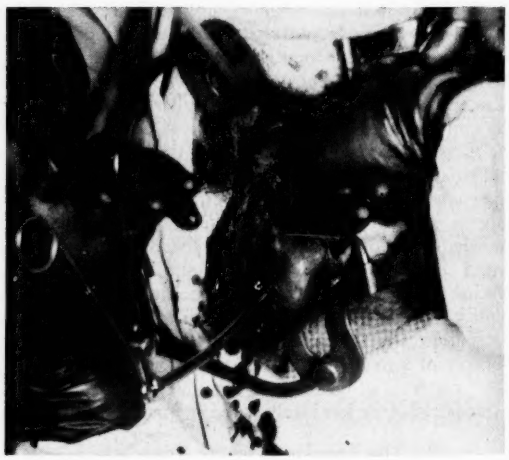

Fig. 3—The dilator in position controlled by left hand. Head of dilator placed in stenotic valve under guidance of index finger in atrium.

dilator is adequate for most valves, commissural division being completed digitally.

If the dilator completely divides the anterior or the posterior commissure without affecting the other, the difficulty arises that in a further attempt the force required partially to detach a cusp may be less than that required to begin division of the remaining commissure. In these circumstances the dilator should probably be abandoned.

When a valve is exceptionally sclerotic the force required to divide the commissures may be so great that much caution is required to avoid damage to the cusps. There is, however, a wide gap between the degree of force which will tear a cusp and that generally required for valvulotomy, and valvular damage without forewarning must be exceedingly rare.

Advantages of the Ventricular Route

Had it not been for a period during which circumstances dictated the passage of the dilator through the ventricle, and for initial difficulty from entanglement of the transatrial dilator in the chordæ tendinæ, we should have followed Dubost in his transatrial approach. Having become accustomed to the transventricular route, however, we find it has considerable advantages.

Placing the dilator requires no special skill. When it has been passed through the ventricular wall it can be immediately palpated with the transatrial finger and set exactly in the valve. In cases in which the atrial approach is in any way difficult—for example, when the auricle is shrunken and fibrotic, when the atrial wall is sclerotic or the pulmonary veins are small—a single introduction of the finger followed by a transventricular manipulation is much less troublesome, particularly in the control of bleeding, than repeated introduction and withdrawal of the finger and instrument through the atrium. This advantage is most noticeable in cases requiring a second valvulotomy in which the auricle is absent or fibrosed and not available for introduction of finger or instrument.

The valve and the head of the dilator can be palpated throughout valvulotomy. One might therefore expect to add precision to the valvulotomy and to detect traumatic incompetence at its very beginning, but in fact remarkably little advantage is gained. Reflux is inevitable during the whole time the dilator is in the valve and incompetence from trauma cannot be assessed until the dilator has been withdrawn. For this reason each use of the dilator must be tentative and sudden wide opening must be avoided.

It seems probable that when the atrium contains clot the single introduction of the finger for exploration of the valve and guidance of the dilator is less likely to dislodge fragments than the manipulations required by any transatrial valvulotomy. Moreover, when the valve is heavily calcified the excrescences are mostly on the atrial surface and less likely to be broken and detached by a ventricular instrument than by the finger or transatrial dilator.

When aortic valvulotomy is to be undertaken at the same operation, the same dilator and the same route may be used.

The ventricular route has few practical disadvantages. It cannot conveniently be used when the approach is through a right thoracotomy, and if for any reason the mitral valve must be explored from the right—as may be convenient, for example, in some cases of second valvulotomy—division of the sternum is necessary to give access to the left ventricle.

The ventricular incision must be at least far enough from the atrioventricular ring to permit the expanding head of the dilator to be completely clear of the ventricular wall when it is opened in the valve. This is easier if the incision is made near the apex and this region is usually the least vascular. In this position there is no likelihood of damage to the anterior papillary muscle or its related chordæ.

The risk of causing ventricular fibrillation by incision of the ventricle appears negligible.

To have two openings in the heart at the same time might make control of both difficult. A finger laid on the ventricular incision is enough for its control. Indeed, within a minute, the ventricle is likely spontaneously to cease bleeding, so that if an atrial tear should occur it could receive undivided attention. The cause of an atrial tear, however, is not usually the mere introduction of the finger but a forceful attempt at digital rupture of the commissures. When this more strenuous part of the valvulotomy is taken over by the dilator an atrial tear is less likely. Because of high ventricular pressure, ventricular bleeding may be more persistent when there is severe aortic valvular disease as well as mitral stenosis, and in these circumstances it is a reasonable precaution to use a purse-string suture for the temporary control of the ventricular incision.

The introduction into the ventricle of clot or a fragment of ventricular muscle by the repeated passage of the dilator is a theoretical hazard which has not been encountered.

Immediate postoperative bleeding is the only complication of the ventricular approach which *may* have been observed, as mentioned above, in a single case. Inadequate suture technique might produce a ventricular aneurysm. This has not been observed but the use of purse-string or mattress sutures for closure of the ventricle has for this reason been avoided and only simple interrupted silk sutures, one at least taking the full thickness of the ventricular wall, have been used.

Unlike the left ventricle in aortic disease, the ventricle in mitral stenosis has not proved friable or difficult to suture.

Extent of Commissural Division

In our records of 1950–52 there are a variety of descriptions of the mitral valve after valvulotomy, indicating sometimes the estimated size of the valve and sometimes the extent of commissural division and hence they are unsuitable for statistical analysis of the extent of valvulotomy. It is certain that in that period few if any commissures were completely divided. Because of the remarkable dissimilarity of the normal mitral valve, palpated as occasion arose during operations on the lung, from the stenotic valve after valvulotomy there was at first no criterion of complete commissural division.

From 1953 onwards the records of commissural division are fairly reliable, although the earlier descriptions probably still tend to exaggerate the extent of division and the incidence of complete division. The type of patient undergoing mitral valvulotomy was changed only by the addition of an increasing proportion of those requiring a second valvulotomy. They presented peculiar difficulties but also, since the return of symptoms appeared in most cases to be related to an inadequate first operation, provided an additional stimulus to the achievement of complete valvulotomy. Table I shows the frequency and extent of commissural division before and after the

transventricular dilator came into use. The figures show that use of the dilator was associated with a striking increase in the incidence of complete anterior and posterior valvulotomy and decrease in the incidence of failure completely to divide either commissure. Since digital valvulotomy had not often effected posterior commissural rupture, and operative attempts had been directed almost exclusively at the anterior, it is not surprising that the use of the dilator which exerted an equal force on both commissures resulted in an increase in the number of cases in which the posterior commissure alone was divided. This number was further increased by early readiness to accept division of one commissure as adequate and awareness of the increased risk when the dilator is used after complete division of one commissure. The estimates of posterior commissural division remain less certain than of anterior division. While the opened anterior commissure is nearly always well defined to palpation, the clear edges of the cusps leaving no doubt that a natural line of cleavage has been followed and that the anterior end of the natural line has been

TABLE I—EXTENT OF COMMISSURAL DIVISION BEFORE AND AFTER INTRODUCTION OF DILATOR

—	Before dilator	After dilator
	No. of cases	No. of cases
Both commissures completely divided ..	29 (*14·5%*)	146 (*28%*)
Only anterior commissure completely divided	105 (*52·5%*)	171 (*33%*)
Only posterior commissure completely divided	14 (*7%*)	148 (*28%*)
Neither commissure completely divided ..	52 (*26%*)	56 (*11%*)
Total	200	521

Records before 1953 are excluded.

reached, the posterior commissure, as felt from the patient's left, usually lacks the same definition. Only the attachment of the chordæ indicates that the line of division is close to the natural line.

Valvular Calcification

The adverse effect of palpable calcification of the valve on the incidence of complete commissural division was less than might have been expected. Before the dilator became available 11 out of 112 (10%) calcified valves had complete anterior and posterior commissural division and afterwards 37 out of 165 (23%) so that the improvement was similar to that which occurred in the whole series. Since heavy calcification is regarded by some as a contraindication to operation a group of 450 cases, consecutively undergoing operation from one medical unit, was examined with reference to the radioscopic estimate of heavy calcification and to the clinical result.

Table II shows that 14% of patients with heavy valvular calcification died of operation. Only 1 of these deaths was from calcific embolism. The pre-dilator group of 25 survivors with heavy calcification was observed for five to nine years after operation. 13 results, or more than half, were classed as good at the end of five years, and 4 as fair having deteriorated from good. It seems highly probable that the results in those treated with the dilator will be better as a consequence of the more extensive commissural division and, as can be seen from table II, the operative mortality is not higher. We should like to emphasise that what may be achieved at operation cannot be forecast at preoperative examination and that operation should not be withheld from any patient because of heavy calcification alone.

TABLE II—DEATHS IN RELATION TO VALVULAR CALCIFICATION

Technique	Total cases	With valvular calcification	With heavy calcification	
			No. of cases	Deaths
Before dilator ..	195	54	30	5
After dilator ..	255	74	40	5
Total ..	450	128 (*29%*)	70 (*16%*)	10 (*14%*)

Prediction of Operability

Sellors et al. (1953) place first in the indications for operation in mitral stenosis "severe stenosis of the mitral orifice, the anatomical conformation of which must be suitable for surgical correction", and state: "We regard the following clinical signs of mitral stenosis as indicative of a pliant diaphragmatic valve amenable to valvulotomy: a snapping apex beat; a snapping first sound (closing snap); and a loud opening snap of clicking quality." This has been widely interpreted as meaning that it is possible not only to recognise preoperatively the type of valve which will give a good functional result, provided that the commissures are divided, but also to forecast the divisibility of the commissures. In our experience many patients who have had a satisfactory valvulotomy followed by prolonged freedom from symptoms have had the signs of a pliant diaphragmatic valve, but there have also been so many exceptions that in the individual case a reliable prognosis cannot be made. The signs of the pliant diaphragmatic valve have been observed when both commissures resisted all efforts at complete division and also when the cusps adjacent to the commissures and orifice were so sclerosed as to impair movement after valvulotomy. Conversely these signs have been absent in cases of tight mitral stenosis, in which both commissures were completely divided and the general mobility of the valve has permitted freedom from symptoms for five years. These findings are still compatible with the view that the signs of the pliant valve are caused by the to-and-fro displacement of the aortic cusp with systole and diastole. The part of the mitral valve which at operation seems least affected by sclerosis in rheumatic

TABLE III—INCIDENCE OF TRAUMATIC MITRAL INCOMPETENCE, ESTIMATED CLINICALLY AFTER OPERATION

—	Total cases	Reflux caused or increased	Incidence of traumatic reflux
Pre-dilator group	184	29	16%
Dilator group	241	45	19%
Total	425	74	17%

disease is usually that part of the aortic cusp farthest from the mitral orifice. It can sometimes be felt moving vigorously with the heart's action when the region of the orifice is rigid. But it is the state of the cusps at the orifice and in the commissures created by their fusion which determines whether valvulotomy can be performed and, to a considerable extent, how well the valve will function postoperatively.

Traumatic Mitral Incompetence

The operative record concerning mitral incompetence has been based on palpation of the regurgitant flow of blood with the gloved finger. Doubtless reflux would have been more frequently recorded if the bare finger had been used but slight reflux is of so little clinical importance that there is no point in the more delicate palpation with the lapse from conventional aseptic care

which it involves. Increase in reflux was recorded when it occurred through newly opened commissures as well as through the stenosed orifice itself. The force and extent of reflux during operation depends upon many factors and varies during a quite short period of observation so that other comment on its severity is inappropriate except at the two extremes. That the frequency of reflux has been inaccurately estimated is borne out by the finding of a mitral systolic murmur postoperatively in patients in whom reflux was not felt at the time (6%) and by the record of reflux when subsequently no murmur could be heard (9%). Presumably this transient reflux was the consequence of distortion of the valve by the palpating finger or some brief valvular dysfunction related to the trauma of valvulotomy. In a few cases reflux was felt before but not after valvulotomy. In most of these there was some obvious cause such as diminution of the vigour of the heart's action but in some no such cause was observed and occasionally there may have been improvement in the coaptation of the cusps.

TABLE IV—REFLUX IN RELATION TO EXTENT OF COMMISSURAL DIVISION

—	No. of cases	No. with palpable reflux
Both commissures completely divided ..	88	21 (24%)
Only anterior commissure completely divided	157	40 (25%)
Only posterior commissure completely divided	82	32 (39%)

Cases before 1953 excluded because of unreliability of record of commissural division. Reflux estimated by palpation during operation.

Again, as in table, II the total number of cases from one medical unit has been analysed. There is no reason to doubt that findings in the rest of the surgical series would be similar. It will be seen from table III that the incidence of traumatic reflux as judged by subsequent systolic murmur or increase in the intensity of a pre-existing systolic murmur was 16% in the pre-dilator group and 19% in the group treated with the dilator.

The increase in incidence of traumatic mitral incompetence is comparable with the increase in frequency of complete commissural division shown in table I.

Table IV shows a higher incidence of traumatic mitral incompetence in cases in which the posterior commissure but not the anterior is completely divided. This relationship has been constant whatever technique of valvulotomy was used.

Considering the degree of sclerosis and deformity of some stenosed mitral valves it would be surprising if valvulotomy regardless of the technique used were not sometimes followed by incompetence whether because of mere liberation of the distorted cusps or because of damage to the cusps or chordæ. Most frequently incompetence has occurred when the surgeon was unaware of having injured any part of the valve.

The operative injuries known to have been produced by the transventricular dilator are of four types.

TABLE V—CAUSES OF DEATH IN 826 CASES

Causes of death	Pre-dilator series (388)	Dilator series (438)	Total (826)
Cerebral embolism	10	6	16
Traumatic mitral incompetence	4	6	10
Cardiac arrest	4	2	6
Hæmorrhage	3	2	5
Circulatory failure	2	3	5
Various	2	3	5
Total	25 (5·0%)	22 (6·4%)	47 (5·7%)

(1) Rupture of a leash of chordæ at its attachment to the aortic cusps.

(2) Detachment of the aortic cusp from the ring anteriorly or posteriorly.

(3) Rupture of the mural cusp close to its anterior or posterior end.

(4) Deviation of the line of commissural section round a sclerotic or calcific nodule lying in the commissure.

Rupture of Chordæ

In 2 cases in which an expanding dilator was passed from the auricle into the mitral valve the head of the dilator became entangled in the chordæ and prolonged efforts at its release ended with rupture of chordæ and severe incompetence. 1 of these patients died in the early postoperative phase. The other survived with symptoms of severe incompetence which persisted for two years and thereafter regressed.

In 1 patient a first trial of the transventricular dilator caused rupture of a leash of chordæ at its attachment to the aortic cusp. This case is unique in that lesion was caused by a gentle manipulation, whereas the other lesions caused by the dilator followed an unduly severe application of force.

Chordæ are not known to have been ruptured by finger or knife but in five cases the first recognition of regurgitation followed separation of fused chordæ. In none was it severe.

Partial Detachment of the Aortic Cusp

This injury is recorded in 6 cases. 1 patient died from detachment of the cusp when the dilator was used after complete posterior commissural division in an attempt to divide a fused anterior commissure. The detachment extended to 4 mm. and was immediately followed by severe reflux. The same mechanism was responsible in 2 more cases. In the remaining 3 the detachment followed the final stroke with the finger to complete commissural division. In none of the survivors was reflux considered severe as judged by palpation or subsequent progress.

Damage to the Mural Cusp

This injury was recorded in 4 cases. In each it followed very forceful use of the dilator but in none was the degree of incompetence severe. The damage was noted as (1) a tag on the edge of the cusp, (2) a notch on the edge of the cusp, (3) division of the cusp near its anterior end, (4) division of the cusp near its posterior end.

Deviation of the Line of Commissural Division

Deviation round a sclerotic or calcific mass in the commissure occurred 3 times, once passing to the aortic side and twice to the mural side.

Since the dilator was used, the incidence of traumatic mitral incompetence has not increased out of proportion to complete commissural division. Incompetence after valvulotomy with the dilator is often produced by the final use of the finger to complete division of a commissure or separation of the chordæ. With the introduction of the transventricular dilator there has developed a more critical appreciation of valvular anatomy and a more careful search both for reflux and for the lesion causing it. This undoubtedly accounts in part for the recorded increase in frequency of incompetence and of valvular damage. It is noteworthy that in that part of the series in which the comparison has been made there has been no concomitant increase in incompetence of dynamic significance, as judged by subsequent clinical examination.

Deaths Related to the Operation

In 826 cases there have been 47 deaths (5·7%) in close relation to operation. 4 of these followed a second valvulotomy. The causes of death and their incidence in cases in which the transventricular dilator was used are shown in table V.

It was hoped that by the reduced need for atrial manipulation in conjunction with the transventricular dilator there would be less tendency to mobilise atrial clot and consequently fewer cases of embolism. Death from cerebral embolism

occurred six times (1·4%) in 438 cases in which the dilator was used while in 388 valvulotomies by other techniques it occurred 10 times (2·6%). The routine intermittent occlusion of the three great branches of the aortic arch in cases of atrial fibrillation, valvular calcification, or past embolism has not affected the incidence of cerebral embolism at operation.

The possibility was envisaged that death from traumatic mitral incompetence would become more frequent with the use of the transventricular dilator. Six deaths (1·4%) were due to this cause in 438 cases in which the transventricular dilator was used and 4 (1·0%) in 388 others. 2 of the 6 cases were second valvulotomies, and in face of a second failure to enlarge the orifice an injudicious degree of force was applied to the dilator causing, in both, damage to the posterior part of the aortic cusp.

Deterioration of the heart's action, ventricular fibrillation, and cardiac arrest appeared, earlier, to be related to strenuous efforts with finger and knife to divide a commissure, and perhaps also to carbon-dioxide retention. Of the 2 cases of arrest after transventricular valvulotomy, 1 came without warning seventy-five minutes after operation and the second after repeated attacks of ventricular fibrillation during thoracotomy, aortic valvulotomy, and mitral valvulotomy.

A case of postoperative hæmorrhage requires mention because of its possible relation to the transventricular route. Intrathoracic hæmorrhage was recognised one hour after operation and the thorax was reopened. No source of bleeding was found but one of four sutures which had closed the ventricular wound was undone and this might possibly have been the cause of the hæmorrhage.

Reoperation

Both the advantages of the transventricular dilator and the dangers of its misuse are exemplified in those cases in which a second valvulotomy has been necessary. There were 32 such cases, presenting after an average of fifty-five months and with a range of nineteen to a hundred-and-one months after the first operation.

In only 2 had a commissure been completely divided at the first operation; in 1 the posterior commissure was still open at the second operation and in the other the anterior commissure was so densely re-fused that its division presented greater difficulty than on the first occasion. This was unexpected since it seemed that comparatively recent adhesions would be lighter than those of longstanding and some commissures which had previously been partially divided were reopened with exceptional ease. In 12 of the 32 cases both commissures were completely divided at the second operation. In 5 neither commissure was completely divided, 2 of these cases being before the dilator was available.

Reflux was produced or increased in 7 cases, in 2 of which it was associated with palpable valvular damage and caused death. Both of these injuries were the result of excessive force applied to the dilator as described above. There were 2 other deaths, making a total of 4.

The close relation between the need for a second operation and an incomplete first operation provides some ground for expecting that in the later cases a second operation will be required in a smaller proportion or at a longer interval after the first.

Summary and Conclusions

The transventricular approach to the mitral valve, using a mechanical dilator, was adopted in 438 patients requiring valvulotomy.

The use of the dilator was associated with a striking increase in the incidence of complete anterior and posterior commissural division and a decrease in incomplete division of both commissures.

The operative mortality has been slightly higher (6·4% compared with 5·0%), but on the other hand more patients have been improved.

Results have been good in a surprisingly high proportion of cases with heavy calcification of the valves.

Death from traumatic mitral incompetence has not been more frequent than with other techniques, but with improved commissural division there has been a slightly higher incidence of postoperative systolic murmurs.

It was concluded that what will be achieved at operation cannot be predicted from preoperative examination.

In our experience the advantages of the use of the transventricular dilator have made it a valuable addition to the techniques of mitral valvulotomy.

REFERENCES

Allen, D. S. (1924) *Arch. Surg.* **8,** 317.
— Graham, E. A. (1922) *J. Amer. med. Ass.* **79,** 1028.
Bailey, C. P. (1949) *Dis. Chest,* **15,** 377.
Baker, C., Brock, R. C., Campbell, M. (1950) *Brit. med. J.* i, 1283.
Bernheim, B. M. (1909) *Johns Hopk. Hosp. Bull.* **20,** 107.
Brunton, L. (1902) *Lancet,* i, 352.
Cutler, E. C., Levine, S. A. (1923) *Boston med. surg. J.* **188,** 1023.
— — Beck, C. S. (1924) *Arch. Surg.* **9,** 689.
Dubost, C. (1954) *Pr. Méd.* **62,** 253.
Harken, D. E., Ellis, L. B., Ware, P. F., Norman, L. R. (1948) *New Engl. J. Med.* **239,** 801.
Logan, A., Turner, R. W. D. (1953) *Lancet,* i, 1007.
Murray, G. (1950) *Canad. med. Ass. J.* **62,** 444.
Sellors, T. H., Bedford, D. E., Somerville, W. (1953) *Brit. med. J.* ii, 1059.
Souttar, H. S. (1925) *ibid.* ii, 603.
Turner, R. W. D., Fraser, H. R. L. (1956) *Lancet,* ii, 525, 587.

TRANSVENTRICULAR MITRAL VALVOTOMY
REPORT OF 50 CONSECUTIVE CASES

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MANY mitral valvotomies still give unsatisfactory results. Like many others, we found that the transatrial finger-fracture method often produces, at best, a limited improvement, and the use of various finger-knives has not always been successful. Many ingenious instruments and procedures have been devised to overcome the resistant valve (Baker et al. 1950, Bailey and Morse 1957, Romanos and Derom 1955, Dubost 1954, Thompson 1954). We were introduced to the transventricular approach to the mitral valve by Logan (1956), and our experience with it began in August, 1957. It had been intended to reserve the method for those cases where finger-fracture of the commissures was difficult or impossible. The first results were so satisfactory, however, that it was subsequently employed in every case. This series comprises the first 50 cases operated on by one of us (H. B. C.).

The Patients

The age-distribution is:

Age	24–34	35–44	45–54	55–65
No. of patients	10	19	17	4

The patients were graded along similar lines to those described by Baker et al. (1952): grade II 9 patients, grade III 34, and grade IV 7. There was no patient in grades O or I. All 3 deaths were in grade IV patients.

In 40 cases, the valvotomy was the first operation, 5 were reoperations, and 1 a third operation. 4 patients had mitral and aortic valvotomies. There were 41 females and 9 males.

15 patients were in established atrial fibrillation before operation, and 1 in persistent auricular flutter. The others were in regular rhythm.

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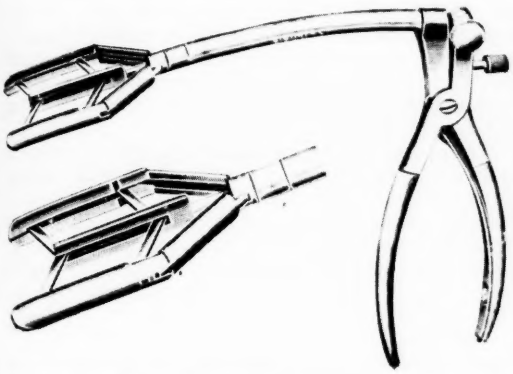

Fig. 1—The Tubbs dilator (Genito-Urinary Manufacturing Co.)

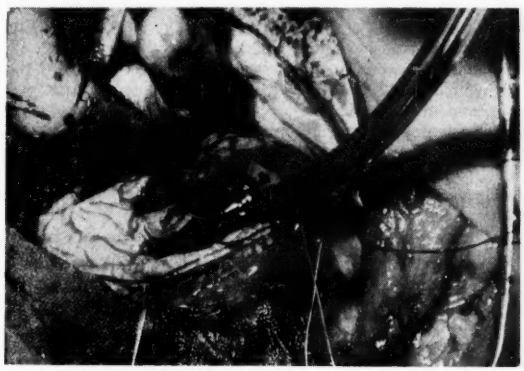

Fig. 2—Right index guiding dilator through mitral orifice immediately before valvotomy.

The Operation

Through a standard lateral thoracotomy incision, the pleural cavity is opened through the bed of the resected 5th or 6th rib. The rib chosen depends on the size of the left ventricle as estimated from the chest X-ray.

The pericardium is opened anterior to the phrenic nerve. A Crafoord clamp is applied at the base of the auricle and an incision made on the distal side to allow eventual insertion of the right forefinger. (In a few cases, where the auricle is small or where there is firm mural clot, and in a reoperation, a purse-string suture in the atrial wall, or in the superior pulmonary vein, is used.) Loose clot is removed by opening the clamp and allowing the blood to flush briefly. A stitch is placed in the ventricle. The right forefinger is now inserted through the incision in the auricle as the clamp is removed, and the mitral orifice palpated. Care is taken to occlude the orifice for the briefest possible time. The size and line of the opening are judged and the finger tip withdrawn into the cavity of the atrium. Using a fine scalpel held in the left hand, a small incision is made in the left ventricular wall between the loop of the stitch previously inserted, and through the opening a Tubbs dilator is inserted (figs. 1 and 2). The instrument has previously been set by the theatre sister to allow dilatation to a diameter estimated when the valve was palpated. This is usually 4 cm. but occasionally less. The point of the instrument is guided through the mitral orifice by the right forefinger from the atrial side, and once in position the blades are opened firmly in the line of the commissures. The dilator is closed and withdrawn, the ventricular stitch being tightened to approximate the margins of the incision. With the right forefinger the commissures are split further if necessary, and the chordæ separated if they are fused, when improved mobility of the valve is at once apparent. The finger is withdrawn from the auricle and the clamp reapplied. The ventricular stitch is tied, and the auricle sutured in two over-lapping continuous layers. Occasionally isolated additional stitches are required. The pericardium is loosely sutured and the chest closed.

Blood-loss is usually small, and some of our cases have not required transfusion.

The patients are nursed in an oxygen tent for the first twelve hours, and are allowed up on the third day. Early activity is encouraged.

All patients have had digitalis before and after operation. The amount of digitalis is reduced to a suitable maintenance dose in those who are in established atrial fibrillation. Patients in regular rhythm have their digitalis only for a few days after operation.

Results

There have been 3 deaths (6%) and it is instructive to consider these cases in detail.

CASE 1.—A woman of 42, grade IV. Clinically severe mitral stenosis with high pulmonary vascular resistance; considerable aortic stenosis. The mitral orifice, less than 1 cm. in diameter, was split easily to 4 cm. The pressure gradient across the aortic valve was reduced adequately by aortic valvotomy. Despite the usual precautions to avoid cerebral embolism, the patient was totally hemiplegic after operation and died on the fourth day. No embolism was found but there was extensive cerebral softening. Both valvotomies were adequate.

CASE 2.—A woman of 65, grade IV. Relatively short history. Gross mitral stenosis clinically. At operation a huge organised clot occupied the left atrium and the palpating finger had to be inserted through a purse-string suture in the atrial wall. Valvotomy by the transventricular route was performed satisfactorily. Postoperatively, cyanosis persisted and the patient died ten hours later. At necropsy the atrial thrombus, 6 cm. in diameter, was found to have ball-valved into the mitral orifice.

CASE 3.—A woman of 49, grade IV. Previous mitral valvotomy (transatrial) three and a half years before, at which split from 1 cm. to 2 cm. was achieved with difficulty, because cusps were fibroelastic. Relief was temporary and eventually reoperation had to be undertaken. The atrium was reached through a purse-string suture across the end of the superior pulmonary vein. The valve diameter was not more than 1 cm. and the cusps thick. Transventricular valvotomy to 4 cm. was easily performed. Unfortunately the patient was over-transfused and died nine hours later in acute cardiac failure. At necropsy, the valvotomy was satisfactory.

The activity of the 47 survivors was estimated so far as possible objectively (8 were operated upon in the past three months and have not been included in the following assessment):

Time since operation	*Activity*	*No. of patients*
6–12 mos	Full	5
	Moderate	3
	Limited	0
13–18 mos	Full	19*
	Moderate	6
	Limited	3
19–24 mos	Full	9
	Moderate	2
	Limited	0

* Includes 2 combined mitral and aortic valvotomies.

By full activity is meant that the patient can perform his or her full normal work without limitation, and enjoy such recreations as walking and dancing. Those patients who have not returned to full work, and in the case of housewives, who do not, for example, perform heavy housework, have been classified as moderately active: in every such case, there has been great improvement and, as might be expected, many of these patients are in established atrial fibrillation.

The three patients whose activity is limited warrant further consideration.

A woman of 46. Third operation, described below. Only slight improvement after the two previous operations, grade IV before the third valvotomy. She can now perform light household duties, and climb stairs without dyspnœa.

A woman of 42, grade IV. Mitral stenosis, aortic incompetence, and organic tricuspid incompetence. Bedridden before mitral valvotomy, and can now go shopping, although ascites, presumably from the tricuspid incompetence, requires occasional paracentesis.

A woman of 53, grade IV. Satisfactory valvotomy, but bilateral deep-vein thrombosis post-operatively, with multiple pulmonary emboli, from which recovery has been incomplete. Not really more active than before operation.

3 patients who previously suffered intermittently from atrial fibrillation, but were in regular rhythm at the time of operation, subsequently lapsed into fibrillation which has proved permanent.

Reoperation

In 5 patients, previous valvotomy had been performed by the atrial route. It is worth noting that, in each, it had been technically impossible to achieve satisfactory valvotomy at the operation, because of extensive calcification, or gross thickening of the cusps. The 4 surviving patients in this group are greatly improved: 3 are fully active.

A further patient (mentioned above) had had two previous unsuccessful operations. At the third operation the atrium was entered via the superior pulmonary vein, and a very calcified, stenotic, and incompetent mitral valve was found. Valvotomy was then achieved easily by the transventricular route and the incompetence not obviously increased.

Aortic and Mitral Stenosis

4 patients suffered from aortic and mitral stenosis, severe enough to justify operation on both valves. The mitral valvotomy was performed first in each case and the dilator withdrawn. Aortic valvotomy was then carried out (Brock 1957).

There was 1 death, described above. Of the remaining patients, the 2 males are in full employment, and the female, aged 61, is fully active.

Complications

There were 2 cases of embolism. The one discussed above was fatal. In the other, obstruction of a retinal vessel caused considerable initial limitation of the visual field of one eye: this is now greatly improved, and the patient is otherwise very fit.

One patient required aspiration of a hæmopericardium on the nineteenth postoperative day. Another patient almost certainly had a hæmopericardium, but recovered without aspiration.

In 3 patients persistent atrial fibrillation developed post-operatively. In each, fibrillation had been present intermittently before operation.

There was no wound sepsis. Blood-loss was never more than moderate, and often slight.

Discussion

In the first case in this series the valve was tightly stenosed, and the cusps thick and unyielding. The transventricular dilator was used rather than persevere with further attempts at finger-fracture from above, and the valvotomy was so satisfactory that succeeding cases were dealt with similarly. The method had some immediate attractions. Valvotomy was quickly achieved and both commissures usually split to a degree not thought possible by transatrial finger-fracture in any but the most favourable cases. Even when calcification was severe, surprisingly complete valvotomy resulted. In most of the reoperations no permanent impression had been made at the first operation on a tough fibroelastic valve, despite considerable perseverance by the older route: by the transventricular route splitting to the valve margins was at once achieved.

The rapidity of the method avoids the dangers of occlusion of the stenotic orifice for all but the briefest interval.

Fused chordæ may be freed and cusps mobilised after valvotomy because the orifice is so adequately opened. Despite the additional incision in it, the heart is handled less because of the brevity of the procedure.

An electrocardiographic monitor showed no serious arrhythmia in any case.

Fears of serious incompetence have not been realised. It seems that if the setting of the dilator proves to be rather wider than necessary, the orifice stretches rather than tears. It is conceivable that when the instrument is passed through the ventricular wall, other than at a point near the apex, the anterolateral papillary muscle might be damaged; or the instrument might pass between the chordæ on one side, so that rupture of one or more chordæ might accompany the valvotomy, the consequent overriding of one cusp resulting in incompetence. These possibilities are avoided by inserting the dilator close to the apex.

It has not been our policy to use the transventricular method after prolonged attempts at finger-fracture have produced a myocardium which is hypoxic and of poor tone. Were we to encounter a valve which split to the margins with the minimum of digital manipulation through the atrium, we would not, of course, proceed to the transventricular approach. It is notable, however, that we have not in these 50 cases had such an experience and we feel that such valves are distinctly uncommon. It is important to proceed at once to the transventricular approach after a rapid assessment of the condition of the valve by the palpating finger. Postoperative progress has been remarkably smooth, and our anæsthetists and nursing staff have been enthusiastic supporters of the method.

For the first few valvotomies penicillin was given over the pre- and post-operative period: there have been no untoward results since it was stopped.

We have not denied operation to any patient whose symptoms might reasonably be expected to improve. Even so, the mortality-rate of 6% bears comparison with various published series: D'Allaines and Blondeau (1955), 7% mortality in 400 cases; Ellis and Harken (1955), 11·6% in 500; and Bailey and Bolton (1956), 7·7% in their first 1000 cases.

An impressive feature has been the excellence of the results in those patients in regular rhythm, many of whom are now fully employed in manual work, often with heart-sounds which are normal or very nearly so. Patients with preoperative atrial fibrillation, and the 3 patients in whom persistent fibrillation developed after the operation, have, all but 1, a greatly improved exercise tolerance. There has been no falling off in the activity of those patients operated upon thirteen to eighteen months ago. The " moderate " patients in this group are 2 of the 3 in whom fibrillation became established after operation.

Summary

In a series of 50 consecutive transventricular mitral valvotomies, with transatrial digital control, there were 3 deaths, all in poor-risk cases.

44 patients improved greatly, and 2 others have limited improvement; 1 is not substantially better, because of postoperative pulmonary embolism.

We should like to express our gratitude to Mr. F. J. Sambrook Gowar in whose unit the patients were treated, and to Mr. P. L. Brunnen, for much help and encouragement. We greatly appreciate the meticulous care with which the sisters and nurses of the Thoracic Surgery Unit, Woodend Hospital, Aberdeen, have nursed these patients.

REFERENCES

Bailey, C. P., Bolton, H. E. (1956) *N.Y. St. J. Med.* **56**, 649, 825.
— Morse, D. P. (1957) *J. thorac. Surg.* **33**, 427.
Baker, C., Brock, R. C., Campbell, M. (1950) *Brit. med. J.* i, 1283.
— — — Wood, P. (1952) *ibid.* i, 1043.
Brock, R. C. (1957) *ibid.* i, 1019.
D'Allaines, F., Blondeau, P. (1955) *Pr. Méd.* **63**, 1361.
Dubost, M. G. (1954) *ibid.* **62**, 253.
Ellis, L. B., Harken, D. E. (1955) *Ann. intern. Med.* **43**, 133.
Logan, A. C. (1956) Conference on Medical and Surgical Cardiology, University of Glasgow, October, 1956.
Romanos, A. N., Derom, F. E. (1955) *Lancet*, ii, 1175.
Thompson, V. C. (1954) *ibid.* i, 710.

ABNORMAL RESPONSE OF ŒDEMATOUS PATIENTS TO ALDOSTERONE OR DEOXYCORTONE

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THE importance of aldosterone in producing the œdema which characterises certain clinical syndromes has been investigated repeatedly during the past few years. Increased amounts of a sodium-retaining substance have been detected in the urine of œdematous patients (Deming and Leutscher 1950, Chart and Shipley 1953, Dyrenfurth et al. 1957), and large amounts of aldosterone have been isolated from the urine of a patient with nephrosis (Leutscher et al. 1955). Many other investigations have established the increase in urinary aldosterone obtained by pH 1 hydrolysis in some cases of congestive heart-failure, nephrosis, and cirrhosis with ascites.

In the course of studies on the effects of large doses of aldosterone administered to normal subjects (August et al. 1958), certain differences between the action of aldosterone in normal and œdematous subjects became apparent and led to the following investigations. Because the amount of aldosterone available was limited, some of the studies were carried out with the sodium-retaining adrenal steroid, deoxycortone. The differences in response between normal and œdematous subjects were similar with either of these sodium-retaining steroids.

Methods

All studies were carried out on the metabolic ward at the Peter Bent Brigham Hospital. Patients received carefully measured diets throughout the period of investigation. Sodium and potassium in urine, and in some cases in fæces, were measured by flame photometer, and urinary excretion of aldosterone by a modification of the method of Neher and Wettstein (Neher and Wettstein 1955, Hernando et al. 1957).

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URINARY SODIUM, POTASSIUM, AND ALDOSTERONE IN NORMAL SUBJECTS AND ŒDEMATOUS PATIENTS GIVEN ALDOSTERONE OR DEOXYCORTONE

Case no.	Diagnosis	Urinary aldosterone (μg. per 24 hr.)		Lowest sodium on therapy (mEq. per 24 hr.)	Urinary potassium excretion on therapy
		Initial	Average on therapy		
1	Normal	15	194	12	Increased
2	Normal	10, 40	128	31	Increased
3	Cirrhosis	28	162	0·3	No effect demonstrable
4	Congestive heart-failure	14	467	2·9	No effect demonstrable
5*	Nephrosis	30	13	0·6	No effect demonstrable
6*	Hypoproteinæmia	—	—	0·8	No effect demonstrable

* Cases 5 and 6 were given deoxycortone, cases 1–4 aldosterone.

Diets were homogenised and checked on several occasions by flame photometry for sodium and potassium content. The aldosterone administered was the *dl*-21-monoacetate which has approximately 50% of the biologic activity of the naturally occurring isomer and was prepared in sesame oil for intramuscular injection.

Results

The results are summarised in the accompanying table.

CASE 3, aged 59, had a long history of increased ephanol intake and ascites of more than a year's duration. He was admitted to another hospital where significant laboratory findings were prothrombin-time 50%, serum-bilirubin 2·96 mg. per 100 ml., serum-alkaline-phosphatase 10·6 Bodansky units, and cephalin flocculation 4+. Liver biopsy on Oct. 21, 1957, showed diffuse nodular cirrhosis. On physical examination the patient was jaundiced, the abdomen was protuberant with shifting dullness and fluid wave, and the liver was palpable 6 cm. below the costal margin.

This patient was transferred to the metabolic ward, Peter Bent Brigham Hospital, and placed on a constant diet with an intake of 10 mEq. of sodium and 116 mEq. of potassium (fig. 1).

After a control period of three days, sodium intake was increased to 78 mEq. per day, and on the seventh day of the study aldosterone in sesame oil was begun at a dose level of 1 mg. intramuscularly every eight hours. This was associated with marked sodium retention and a gain in weight; there was little effect on potassium excretion. Total weight gain was

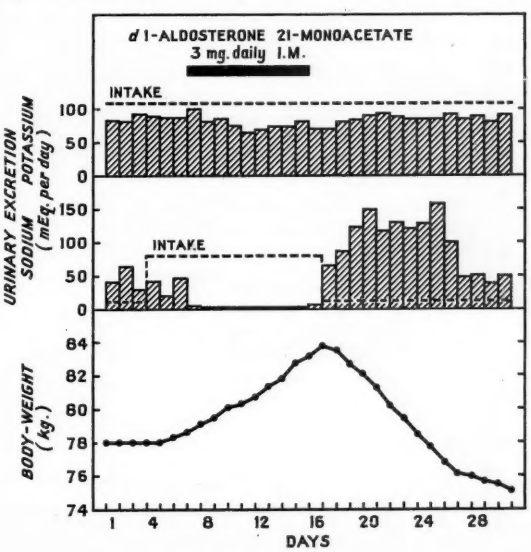

Fig. 1—Findings in case 3.

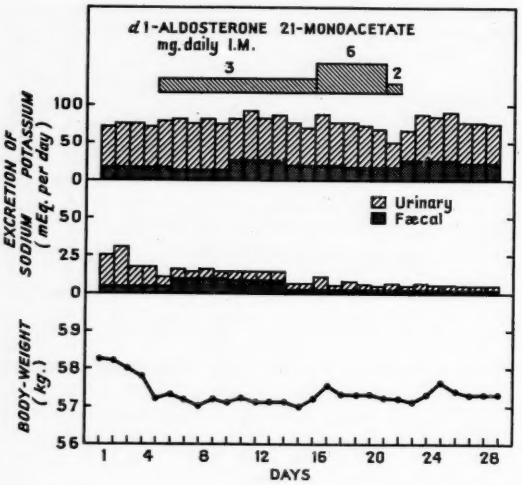

Fig. 2—Findings in case 4.

5·8 kg., which was followed by pronounced sodium diuresis and loss of weight following discontinuation of the aldosterone.

CASE 4 was a 77-year-old white man with symptoms and signs of congestive heart-failure. These improved on bed rest and a constant dietary intake of 10 mEq. sodium and 106 mEq. potassium (fig. 2). On this diet, the patient had a small sodium diuresis with a loss of approximately 1 kg. in bodyweight over four days. At this point, aldosterone was begun at a dose level of 1 mg. every eight hours, and on the sixteenth day of the study this was increased to 2 mg. every eight hours. Sodium excretion fell greatly, reaching a low point of 3 mEq. There was no significant change in potassium excretion and weight remained fairly constant throughout the period of aldosterone administration. When therapy was discontinued there was no significant change in potassium excretion.

CASE 5 was a 57-year-old white man admitted with a chief complaint of œdema with swelling of the abdomen, scrotum, and penis. Urine albumin was 4+ and blood-urea-nitrogen 25 mg. per 100 ml. Serum-protein 3·2 g. (albumin 1·5 g.) per 100 ml. and serum-cholesterol 615 mg. per 100 ml. Renal

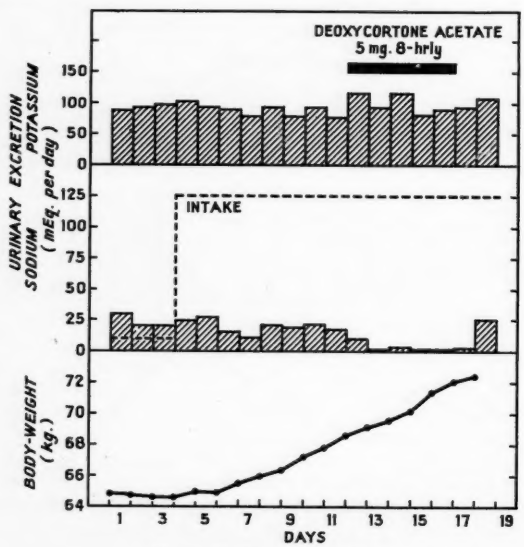

Fig. 3—Findings in case 5.

biopsy revealed changes consistent with renal arteriosclerosis and nephrosis. Blood-pressure 140/70 mm. Hg.

The patient was placed on a diet containing 10 mEq. sodium and 143 mEq. potassium, and on this diet he had diuresis with body-weight falling from 71 to 64·7 kg. On return to a sodium intake of 125 mEq. daily, sodium retention occurred, and body-weight rose to 67·8 kg. (fig. 3). At this point, 5 mg. of deoxycortone acetate, every eight hours intramuscularly, was instituted. Before this, although there was significant sodium retention, urinary sodium averaged 17 mEq. daily. During treatment with deoxycortone the mean urinary sodium was less than 1 mEq. per twenty-four hours on the same sodium intake. Weight increased to 72·4 kg.—making for a total weight gain on added salt and deoxycortone of 7·7 kg., without any indication of "escape" from the renal sodium-retaining effects of the steroid.

CASE 6 was a 58-year-old married white man who gave a one-year history of œdema of the legs and swelling of the abdomen.

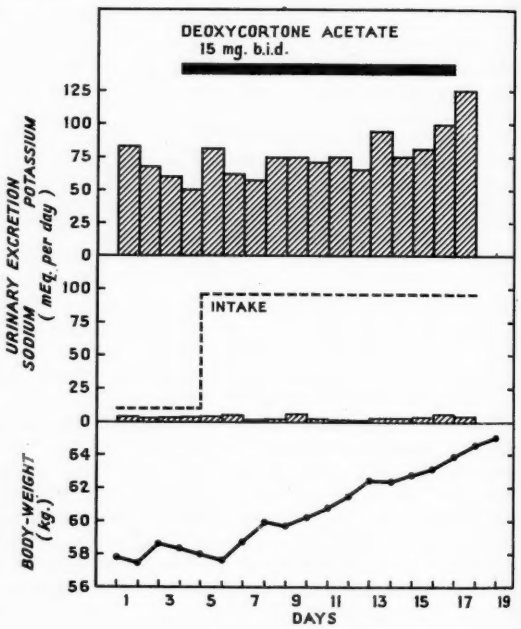

Fig. 4—Findings in case 6.

He reported excess intake of alcohol, up to a pint of whiskey a day, for fifteen years. The abdomen was greatly protuberant, and considerable œdema of the lower extremities was present. Blood-pressure 130/65 mm. Hg. Laennec's cirrhosis and vitamin deficiency were diagnosed initially, but liver biopsy showed only some fatty infiltration and not much evidence of fibrosis. Serum-bilirubin was 0·1 and 0·5 mg. per 100 ml. Bromsulphalein was 0 and 1%. Total plasma-proteins by electrophoresis were 3·7 g. per 100 ml. and plasma-albumin 1·03 g. per 100 ml. Further investigation demonstrated a definite malabsorption syndrome with decreased vitamin-A and butter-fat tolerance and xylose absorption. X-ray of the small bowel showed a picture "compatible with clinical impression of sprue". Biopsy of small intestine was also thought to be "compatible with non-tropical sprue". Incomplete results, with a study of ^{131}I-tagged albumin, suggested increased rate of breakdown of this substance. The œdema in this patient was thus thought to be largely due to hypoproteinæmia as the result of poor nutrition, and possibly increased albumin degradation. Fig. 4 shows the effect of administering 15 mg. deoxycortone intramuscularly b.i.d. to this patient. Weight increased by approximately 7 kg., while sodium excretion remained at a very low level despite a great increase in

intake. Again there was no demonstrable increase in potassium excretion following the administration of deoxycortone.

Discussion

A previous study (August et al. 1958) demonstrated the metabolic changes produced by large amounts of aldosterone administered to normal subjects. The chief effects were threefold: (1) initial sodium retention followed by " escape " characterised by return to approximate daily sodium balance during continued hormone administration, (2) increased urinary potassium excretion, and (3) moderate increase in diastolic blood-pressure.

In the investigation the response to aldosterone or deoxycortone by patients with œdema was notably different, as follows: (1) sodium retention was greater, (2) no " escape " occurred, and (3) urinary potassium excretion did not increase.

The almost complete renal retention of sodium which characterised patients in this study was not produced by either aldosterone or deoxycortone given to normal subjects (August et al. 1958, Relman and Schwartz 1952), or patients with Addison's disease (August and Nelson 1959). A similar pronounced sodium-retaining effect was seen by Davis et al. (1953) in dogs with constrictions around the thoracic inferior vena cava given deoxycortone. The failure of aldosterone or deoxycortone to produce a similar degree of sodium retention in non-œdematous subjects, when even larger doses of hormone were given, suggests another mechanism potentiating the effect of the steroid on total renal tubular reabsorption of sodium. Decreased glomerular filtration with resultant decreased sodium may partly explain this effect.

Although the ability of patients such as those studied to retain large quantities of fluid and electrolytes is well recognised, the reason for continued retention of sodium and chloride with progressive œdema formation is much less clear. When aldosterone was given to normal subjects or to patients with Addison's disease, cumulative salt and water retention ceased after weight gain of about 3 kg., independent of the period during which the hormone was given (Relman and Schwartz 1952, August et al. 1958, August and Nelson 1959). The weight gain of patients in this study considerably exceeded that in the normal or addisonian subjects, but there was no evidence of eventual increase in urinary sodium output. This difference in the response to aldosterone may be due to pooling of fluid in extravascular as opposed to intravascular compartments in these patients. But even if this explanation proves correct, the differences in fluid pooling and the mechanism for the " escape " in normal subjects will remain unexplained.

Potassium depletion is a characteristic feature of hyperaldosteronism, whether due to production of the hormone by the adrenal gland (Conn and Louis 1956) or to exogenous administration (August et al. 1958). Failure of urinary potassium to increase in patients with " secondary hyperaldosteronism " treated with sodium-retaining steroids, therefore, deserves further explanation. Seldin et al. (1951) and Relman and Schwartz (1952) demonstrated the dependence of the potassium-excreting effect of deoxycortone on adequate sodium intake. Thus, animals or men placed on a very low sodium diet fail to lose potassium in the urine when deoxycortone is given. In a similar manner, as shown by these studies, aldosterone appears unable to produce a negative potassium balance in œdematous patients who excrete very small quantities of sodium in the urine. The present cases, except case 4, who had congestive heart-failure, were receiving adequate amounts of sodium in the diet, but excreted almost none in the urine.

These data suggest that aldosterone has two sites of action in the kidney. In the present cases we suggest that almost all of the filtered sodium was reabsorbed proximal to the point in the renal tubule where cation exchange occurs. In the absence of sodium in the tubule at a more distal point, aldosterone could not produce exchange with potassium and increase urinary potassium loss. In normal subjects such exchange did occur and negative potassium balance resulted. If this postulate is correct, we must conclude that in the œdematous patient increased sodium reabsorption is produced by aldosterone proximal to the point in the renal tubule where sodium-potassium exchange takes place: in normal subjects, treated with the same or larger doses of aldosterone, a considerable amount of sodium would pass through this segment of tubule without being reabsorbed, whereas in many œdematous patients, and particularly in such patients treated with aldosterone or deoxycortone, almost complete sodium reabsorption occurs. But availability of sodium in the tubule is the sole mechanism, not for potassium excretion generally, but only for aldosterone-induced potassium excretion. Sodium depleted animals have been shown to excrete a potassium load normally (Anderson and Laragh 1958).

Summary

Aldosterone or deoxycortone was administered to four œdematous patients with congestive heart-failure, cirrhosis and ascites, nephrosis, and hypoproteinæmia, and the effects were compared with those in a group of normal subjects or patients with Addison's disease.

Three chief differences were noted: (1) sodium retention was more nearly complete in the œdematous group; (2) in this group there was no secondary " escape " from the renal sodium-retaining effects of the steroid as there was in the normal group; (3) although increased urinary potassium excretion is common in treated normal subjects, this was not demonstrable in the œdematous patients.

The lack of " escape " from renal sodium retention and the completeness of sodium reabsorption, with failure to excrete greater than normal amounts of potassium, indicate an abnormal response to aldosterone in œdematous patients.

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REFERENCES

Anderson, H. M., Laragh, J. H. (1958) *J. clin. Invest.* **37,** 323.
August, J. T., Nelson, D. H. (1959) *ibid.* (in the press).
— — Thorn, G. W. (1958) *ibid.* **37,** 1549.
Chart, J. J., Shipley, E. S. (1953) *ibid.* **32,** 560.
Conn, J. W. Louis, L. H. (1956) *Ann. intern. Med.* **44,** 1.
Davis, J. O., Howell, D. S., Southworth, J. L. (1953) *Circulation Res.* **1,** 260.
Deming, Q. B., Leutscher, J. A., Jr. (1950) *Proc. Soc. exp. Biol., N.Y.* **73,** 171.
Dyrenfurth, I., Stacey, C. H., Beck, J. C., Venning, E. H. (1957) *Metabolism,* **6,** 544.
Hernando, L., Crabbe, J., Ross, E. J., Reddy, W. J., Renold, A. E., Nelson, D. H., Thorn, G. W. (1957) *ibid.* p. 518.
Leutscher, J. A., Jr., Dowdy, A., Harvey, J., Neher, R., Wettstein, A. (1955) *J. biol. Chem.* **217,** 505.
Neher, R., Wettstein, A. (1955) *Acta endocr., Copenhagen,* **18,** 386.
Relman, A. S., Schwartz, W. B. (1952) *Yale J. Biol. Med.* **24,** 540.
Seldin, D. W., Welt, L. G., Cort, J. (1951) *J. clin. Invest.* **30,** 673.

AMODIAQUINE AND HYDROXYCHLOROQUINE IN RHEUMATOID ARTHRITIS

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SINCE 1951, when Page described improvement in arthritic symptoms in patients with rheumatoid arthritis treated for discoid lupus with mepacrine, various antimalarial drugs have been tried in polyarthritis. In many series a high percentage of cases benefited; but this was largely offset by toxic symptoms, which were sometimes serious.

Material and Method

In this paper we describe 36 cases of rheumatoid arthritis treated with alternating courses of hydroxychloroquine sulphate (' Plaquenil '), amodiaquine (' Camoquin '), and control tablets. They have been seen each month for twenty-four or more months. When in 1958 Hobbs and Calnan and then Zeller and Diering reported corneal opacities in some patients undergoing antimalarial therapy, we decided to make a special study of this complication. There was 1 fatality, probably from agranulocytosis due to amodiaquine.

Hydroxychloroquine was selected as one of the least toxic antimalarials, and amodiaquine as a potent antimalarial which had not been known to produce blood dyscrasias. Each month the patients were questioned as to toxic symptoms and asked to evaluate their condition on a percentage basis and the sphygmomanometer-grip test was applied. The initial dose of hydroxychloroquine was 400 mg., and this was later doubled. The initial dosage of amodiaquine was 400 mg. daily, but, because toxic sequelæ were very common though the effect on the joints was satisfactory, this was later halved. The usual period before therapy was changed was about three months.

Results

Therapeutic Effect (*table I*)

While taking the control tablets only 2 patients improved. With 400 mg. hydroxychloroquine daily, 21 showed slight improvement, 2 much improvement, and 9 no change. Of 10 patients given 800 mg. hydroxychloroquine 5 showed some improvement and 5 much improvement. In 25 periods on 400 mg. amodiaquine 14 showed moderate remission, and 8 considerable remission; 3 showed no change. With 200 mg. amodiaquine, in 21 periods, 11 showed moderate remission and 8 considerable remission; 2 were unchanged.

Much improvement was seen therefore in 50% of patients having 800 mg. hydroxychloroquine per day, in 30–40% having amodiaquine, but in only 6% having 400 mg. hydroxychloroquine. Improvement was usually seen by the fourth week, but it occasionally started earlier.

TABLE I—THERAPEUTIC EFFECTS

Drug	Total no. of periods	Much improvement	Slight improvement	% improvement	No change
Amodiaquine 400 mg.	25	8 (*32%*)	14	88	3
Amodiaquine 200 mg.	21	8 (*40%*)	11	90	2
Hydroxychloroquine 800 mg.	10	5 (*50%*)	5	100	0
Hydroxychloroquine 400 mg.	32	2 (*6%*)	21	72	9
Controls	33	Nil	2	6	31

TABLE II—TOXIC SYMPTOMS DURING PERIODS OF TREATMENT WITH ANTIMALARIAL DRUGS AND CONTROL

Drug	Total	Digestive			Giddiness	Headache	Fatigue	Rash	Visual symptoms
		None	Severe	Slight					
Amodiaquine 400 mg.	25	5	4	8	7	2	2	1	8
Amodiaquine 200 mg.	21	10	1	6	3	1	1	1	1
Hydroxychloroquine 800 mg.	10	8	0	2	0	0	0	0	0
Hydroxychloroquine 400 mg.	30	24	0	3	2	0	1	0	3
Total	86	57	5	19	12	3	4	2	12
Control	33	32	0	1	0	0	0	0	0

On changing from any of the antimalarials to the control tablets 24 of 29 cases relapsed within four months; 16 of these showed signs of deterioration in four to six weeks.

Toxicity (*table II*)

Generally speaking, toxic symptoms varied directly with the relief of rheumatic symptoms, but in many patients malaise was so slight that it was not noticed until control tablets were given. They would then remark that they felt fitter but had more pain. Some patients had much relief without toxic symptoms. Very few had definite toxic symptoms without some amelioration of the joint condition.

Unpleasant symptoms disappeared within a week of stopping the antimalarial drug, except for the 1 patient who died, 1 with a rash, and 1 with nausea and vomiting in whom a month elapsed before return to normal. Only 5 of the 25 patients treated with 400 mg. amodiaquine daily were completely free from toxicity, but 10 of the 21 on half the dose felt well. On the other hand, 8 out of 10 patients tolerated 800 mg. hydroxychloroquine well. 32 out of 40 patients having hydroxychloroquine, therefore, had no toxic symptoms.

During 86 periods on these antimalarial drugs, 24 patients had gastric symptoms (severe in 5), 12 had slight giddiness, 3 had headache, 4 had fatigue, 2 had a rash, and 12 had misty vision or saw haloes around lights.

TABLE III—RESULTS OF SLITLAMP EXAMINATION DURING PERIODS OF TREATMENT

Drug	Total examined	Slight	Severe	Normal
Amodiaquine 400 mg. ..	19	8	5	6
Amodiaquine 200 mg. ..	17	4	4	9
Hydroxychloroquine 800 mg.	1	1	0	0
Hydroxychloroquine 400 mg.	29	8	5	16
Total	66	21	14	31
Control..	10	0	0	10

There was a tendency for minor toxic symptoms to decrease, and for fatigue and mild headache, giddiness, and dyspepsia to disappear, but definite eye symptoms tended to increase.

Corneal Opacities (*table III*)

Sixty-six slitlamp examinations were made on 32 patients during the course of antimalarial treatment.

In 18 patients examination was persistently negative despite continuous medication for up to six months. The other 14 had deposits in the corneal epithelium, but in only 8 were there any symptoms. Only 1 patient who had hydroxychloroquine alone showed considerable opacity. 2 developed depositions while having amodiaquine, though there were none after a course of hydrochloroquine. There was no direct relation between dosage and deposition; but 2 patients, having 400 mg. of amodiaquine daily, who had major changes which cleared, had only minor changes after having 200 mg. for the same period. The deposits tended to increase if the drug was continued. 13 patients with severe ophthalmic changes were observed monthly after being given control tablets, and in all

the deposits steadily decreased. In 3 they disappeared in a month, in 8 in four months, and in 2 in six months. There was no direct relation between eye signs and symptoms, 6 having gross signs with no symptoms, and 3 having symptoms of misty vision or " haloes " with only slight changes on slitlamp examination.

The ocular findings in this series present a picture which, though variable, is characteristic. The intensity of the epithelial deposits seems to be unrelated to dosage or duration of treatment; similar wide individual variations were noted by Hobbs and Calnan (1958). The explanation may lie in constitutional factors as yet undetermined. A remarkable and comparable disparity also exists between symptoms and signs.

Examination by slitlamp (corneal microscope) is essential to detect all but gross changes, and this must be carried out by an ophthalmologist well versed in such techniques and alerted to the possibility. Some typical corneal changes in this series were passed as normal by other observers.

The slitlamp examinations made during this trial failed to reveal any case of definite corneal œdema as in mepacrine toxicity. In a few early cases there was a suggestion of " milkiness " before deposits could be seen with any degree of magnification. Despite detailed searching no changes were seen in any ocular tissue other than the cornea. With the exception of 3 cases showing fine pigment dusting of the posterior corneal endothelium (which was probably irrelevant) all changes were confined to the anterior $^1/_{10}$ of the 0·6 mm. thickness of the cornea. The deposits seemed to lie deep to the superficial squamous cells, and to be in the polygonal-celled lamellæ, the columnar cells, or Bowman's membrane (anterior elastic lamina).

The early changes of amorphous tiny white dots usually progress with continued medication to show a curious linear distribution; this has been likened (Hobbs and Calnan 1958) to the lines of force of a magnetic field, but in many cases there is a curious whorl-like confluence of these lines just below the centre of the cornea. As the changes become more intense, the fine deposits become yellow and then golden brown, and sometimes there are single very dark lines resembling the streaks known by ophthalmologists as Hudson's lines. In a few cases conjunctival lymphatics at the limbus have shown cheesy-looking deposits without pigmentation, but their relevance has not yet been determined precisely.

Idiosyncrasy

Blood dyscrasias are not common with antimalarial drugs, but according to Hodgkinson (1955) they occur occasionally with quinine, pentaquine, and mepacrine, but not with chloroquine or amodiaquine. With quinine leucopenia, which returns to normal when the drug is stopped, is not uncommon, but 4 cases of agranulocytosis and thrombocytopenic purpura have been recorded. Aplastic anæmia is known to occur with mepacrine, and 6 cases are recorded of acute onset with fever and jaundice, and with peripheral granulopenia following later.

In our series 1 patient became acutely ill with jaundice, fever, and agranulocytosis, eight weeks after starting amodiaquine 400 mg. daily; she was admitted urgently to another hospital and died. Apart from this, leucopenia was seen temporarily only once in a patient having amodiaquine, whose total white cell-count dropped to 3500 per c.mm. (with a normal differential count) but returned to 5600 within a month without change of medication.

Discussion

In 1951, the same year that Page recorded improvement in the arthritis of 2 patients treated with mepacrine, Brennicke et al. described the results of treating 38 cases of rheumatoid arthritis with primaquine; 20 improved, but the toxic sequelæ were considerable. Since then many workers have used various antimalarial drugs in rheumatoid arthritis with various degrees of benefit and toxicity.

Hayden (1953) claimed relief with minimal complications in 21 out of 28 cases treated with chloroquine; Erlandsson (1955) found benefit from quinacrine in 6 out of 12 cases; Freedman (1956), using chloroquine, found improvement in 46 of 50 cases with no toxicity; Bagnall (1957), with chloroquine, in 88 of 125 cases, with 10% toxicity; Scherbel et al. (1958), with chloroquine and hydroxychloroquine, in 81 of 157 cases, with very few complications; Engeset (1958), with quinacrine, in 34 of 41 cases, with 3 gastric, 3 psychotic, and 4 skin complications; and Field and Horwich (1958) used chloroquine in 32 out of 39 cases with no major toxic symptoms. Cohen and Calkins (1958), in 22 cases, found 70% improved with chloroquine, against 6% of the controls; but there were 4 cases of severe dyspepsia, 2 of leucopenia, and 1 of psychosis. Buchan (1959) concludes from his experience with 38 cases on chloroquine that the drug was undoubtedly weakly effective in rheumatoid arthritis, and there were few side-effects, none of which was serious.

Some observers have recorded ophthalmic sequelæ of antimalarial therapy. Chamberlain and Boles (1946) and Reese (1946) noted œdema of the cornea with mepacrine, and in 1947 Mann found yellow deposits in the superficial layer of the cornea in mepacrine workers. Hobbs and Calnan (1958) first recorded white or yellow dots seen on slitlamp examination in the corneal epithelium of 28 patients with visual disturbances, who were under treatment with chloroquine; in 1 there seemed to be " continued loss of visual acuity for some time after cessation of treatment ". In 1958 Zeller and Diering reported 10 cases treated with chloroquine, who developed white or yellowish deposits as discrete dots or linear opacities in the corneal epithelium, which were usually central and just below the pupil. Not all these patients had symptoms, and visual acuity was not affected. There was no œdema or conjunctivitis, and the condition tended to regress on cessation of the medication. In some, slight fluorescence with ultraviolet light suggested that the deposits might be of chloroquine. There was no direct relation with dosage or duration of treatment. Hobbs, Sorsby, and Freedman (1959) have described 3 cases of retinopathy with macular degeneration, probably secondary to vascular spasm, in patients treated for about three years with chloroquine.

There seems no doubt that the antimalarial drugs we tested had a temporary beneficial effect on many cases of rheumatoid arthritis. Improvement started in the majority after about four weeks. The threshold of mild toxicity was frequently very near, or overlapping, the therapeutic dosage, but with many patients the benefit far outweighed any mild side-effects, which tended to decrease with continued administration. The original dose of 400 mg. of amodiaquine was definitely too high, and equal benefit with less untoward symptoms was obtained with 200 mg. per day. The best effect with lowest toxicity was obtained with 800 mg. of hydroxychloroquine—400 mg. proving too small. With 800 mg. of hydroxychloroquine 50% of patients showed much improvement, and all claimed some benefit; 20% developed slight digestive disturbances, but there were no serious toxic symptoms. There was a tendency to relapse within four to sixteen weeks of stopping the drug, but 16% seemed to be in true remission.

Slitlamp examinations of the cornea showed depositions in 47% of patients treated with amodiaquine or hydroxychloroquine, but they seemed less likely with the latter.

If the drug was continued the deposit tended to increase, but there were symptoms of misty vision and haloes around lights in only 57% with such deposits. On stopping the antimalarial, the opacities decreased and had disappeared completely in four months in 11 out of 13 patients with gross changes, and in all cases in six months. These corneal changes can be a real hazard if not observed. They are not serious if not neglected, and appear in only less than half the patients having amodiaquine, and in a still smaller proportion having hydroxychloroquine.

There seems little doubt that the fatality was caused by agranulocytosis due to amodiaquine. This patient was having the higher dosage (400 mg.) which is certainly not advisable, and if the agranulocytosis had been "spotted" earlier, and treated adequately with antibiotics and steroids, death might have been avoided.

Hydroxychloroquine in a dosage of 800 mg. per day is probably a useful form of therapy in certain cases of rheumatoid arthritis, but watch must be kept for corneal opacities. Although agranulocytosis has never been recorded during administration of this drug, it has not been used in sufficient cases for long enough to rule out the possibility of this risk.

Summary

36 patients with rheumatoid arthritis were treated for about two years with alternating courses of amodiaquine ('Camoquin'), hydroxychloroquine ('Plaquenil'), and control tablets.

Amodiaquine 400 mg. per day produced severe side-effects; but of 21 patients having 200 mg. 8 improved considerably and 11 moderately; 10 showed no toxic signs, and in only 3 had the drug to be stopped on this account.

Hydroxychloroquine 800 mg. per day gave some benefit in all of 10 cases, and 5 improved greatly. Out of 40 courses of hydroxychloroquine 8 patients had some toxic symptoms, and in 1 the drug had to be stopped.

The main toxic symptoms were dyspepsia and vomiting, giddiness, headache, and visual disturbances.

Improvement in the arthritis usually started after about four weeks and continued for four to twelve weeks after treatment was stopped, but 5 patients continued in remission for about six months.

Corneal opacities were seen in 14 out of 32 cases after antimalarial treatment, though symptoms of mistiness of vision and haloes around lights were present in only 8. They were less frequent after hydroxychloroquine. They always tended to decrease, and in 12 cases had disappeared four months after termination of therapy. Continued treatment tended to increase the deposits.

In 1 case it seems probable that death was due to agranulocytosis caused by amodiaquine medication.

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REFERENCES

Bagnall, A. W. (1957) *Canad. med. Ass. J.* **77**, 182.
Brennicke, F. E., Alving, A. S., Arnold, J., Berganstal, D. M., de Wind, L. T. (1951) *J. Lab. clin. med.* **38**, 795.
Buchan, J. F. (1959) *Ann. phys. Med.* (in the press).
Chamberlain, W. P., Boles, D. J. (1946) *Arch. Ophthal.* **35**, 120.
Cohen, A. S., Calkins, E. (1958) *Arth. & Rheum.* **1**, 297.
Engeset, A. (1958) *Acta rheum. scand.* **4**, 28.
Erlandsson, F. (1955) *Ugeskr. Læg.* **117**, 1677.
Field, H., Horwich, L. (1958) *Brit. med. J.* ii, 1199.
Freedman, A. (1956) *Ann. rheum. Dis.* **15**, 251.
Hayden, G. G. (1953) *Amer. J. med. Sci.* **225**, 71.

References continued at foot of next column

AN ANÆSTHETIC TECHNIQUE FOR PROSTATECTOMY

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PATIENTS who need prostatectomy are particularly susceptible to the toxic effects of many anæsthetic drugs—e.g., persistent curarisation, apnœa, or postoperative respiratory impairment with resultant chest complications. They often have respiratory or cardiovascular disease, obesity, or disturbances of fluid balance. They usually have atheromatous changes in the vascular system, and are intolerant of both blood-loss and rapid or excessive blood-transfusion.

Such patients tolerate hypoxia poorly, and must on no account be deprived of a plentiful supply of oxygen and an adequate cerebral circulation. Gardner (1958) has suggested that emphysema, with a consequent high plasma-carbon-dioxide tension, may cause persistent apnœa when carbon dioxide is washed out of the circulation by vigorous controlled respiration with a carbon-dioxide absorption technique.

Spinal analgesia may cause occasional neurological sequelæ, and it is not always practicable as the sole method of anæsthesia in a disturbed senile patient. The same applies to lumbar epidural block, which is both difficult and time-consuming.

Epidural block by the caudal approach now has an established place in anæsthesia for obstetrics, cystoscopy, and transurethral operations on the bladder and prostate, having largely displaced low spinal block. Though easy to perform and reliable, it will not give adequate analgesia for open operations on the prostate unless excessive local anæsthetic is used, and even then analgesia of the anterior abdominal wall is uncertain. Epidural block can be induced together with abdominal-field block (although not suitable for any second-stage prostatectomy), or with general anæsthesia, relatively light anæsthesia being adequate as the caudal block prevents the shock-producing stimuli during enucleation of the prostate.

We here describe a technique, evolved with the above factors in mind, which we have used in 50 consecutive prostatectomies at the Dreadnought Seamen's Hospital and the Royal London Homœopathic Hospital.

There were no emergency prostatectomies in the series, acute retention being treated by preoperative drainage through either an indwelling urethral catheter or a Riches' suprapubic catheter. The ages ranged from 55 to 86 years, with an average of 71·6 years.

The Technique

The general principle underlying our technique is the combination of caudal block, using 1·5% lignocaine with 1/80,000 adrenaline in a dosage of 15–25 ml., with general anæsthesia, using a little thiopentone for induction, and nitrous oxide and oxygen reinforced by a mixture of chlorpromazine, promethazine, and pethidine, with small doses of either tubocurarine or gallamine for relaxation.

DR. KERSLEY, MR. PALIN: REFERENCES—*continued*

Hobbs, H. E., Calnan, C. D. (1958) *Lancet* i, 1207.
— Sorsby, A., Freedman, A. (1959) *ibid.* ii, 478.
Hodgkinson, R. (1955) M.D. thesis.
Mann, I. (1947) *Brit. J. Ophthal.* **31**, 40.
Page, F. (1951) *Lancet* ii, 755.
Reese, F. M. (1946) *Bull. Johns Hopk. Hosp.* **78**, 325.
Scherbel, A. L., Harrison, J. W., Atdjian, M. (1958) *Cleveland Clin. Quart.* **25**, 22.
Zeller, R. W., Diering, D. (1958) *J. Amer. med. Ass.* **168**, 2263.

TABLE I—PREOPERATIVE AND POSTOPERATIVE MORBIDITY

—	Trans-vesical	Retro-pubic	All open opera-tions	Endo-scopic	Total
Preoperative treatment:					
Good	16	2	18	1	19
Fair	11	5	16	2	18
Poor	8	4	12	1	13
Total	35	11	46	4	50
Left hospital without complication:					
In less than 3 weeks	22	3	25	3	28
In 3–6 weeks	5	2	7	0	7
Discharge delayed by:					
Pulmonary embolism	0	1	1	0	1
Pneumonia	1	1	2	0	2
Postoperative chest complications	2	1	3	0	3
Cardiovascular disease	0	1	1	0	1
Urological complications	4	2	6	0	6
Deaths in hospital:	1	0	1	1	2
Average stay in hospital (days):*	19	34	23	7	21

* Excluding the 2 deaths.

Chlorpromazine and promethazine potentiate the narcotic properties of pethidine and thiopentone without increasing correspondingly their respiratory depressant actions (Hopkin and Brown 1958), and they reduce the amount of relaxant required (Baxter et al. 1954). In the elderly the fall in blood-pressure after chlorpromazine is less transient and less sudden than after thiopentone. The hypotension thus produced is readily influenced by posture, providing an easy and apparently safe method of reducing operative blood-loss, and hence the volume of blood-transfusion required. This direct shock-sparing action of chlorpromazine is probably important only if the caudal block is not entirely satisfactory.

Preoperative Preparation

Cases for prostatectomy are usually admitted to hospital several days before operation.

Breathing exercises are started immediately, and most patients have a preoperative chest radiograph and electrocardiogram; the hæmoglobin, packed-cell volume, and blood-urea are estimated, and, except for cases in which only a transurethral operation is to be done, a pint of blood is cross-matched.

All patients were seen personally by the anæsthetist concerned, and their physical condition was classified in relation to age and capacity for leading a normal life as good, fair, or poor. This classification can be seen in relation to age and operation in tables I and II.

All those for whom the surgeons proposed operation were accepted by the anæsthetists, although operation was postponed for 3 or 4 weeks for medical treatment when necessary. The principal indications for this were congestive cardiac failure, previous coronary occlusion or cerebrovascular accident, present active acute or chronic pulmonary disease, and hypertension greater than 200/100 mm. Hg.

Anæsthesia

The usual premedication of atropine gr. $^1/_{100}$ (0·6 mg.) combined with either morphine gr. $^1/_6$ (10 mg.) or pethidine 100 mg. was given $1^1/_2$ hours before operation.

In the anæsthetic room caudal block was performed, with full aseptic technique, the caudal set and the ampoule of lignocaine being sterilised by autoclaving (Whittet 1954). The prone position with the abdomen supported by pillows was usually employed except in the very obese or very frail, when the lateral position was adopted.

TABLE II—MORTALITY AND MORBIDITY RELATED TO AGE

Age (yr.)	Preoperative assessment			No. of cases	No. of deaths	Average stay in hospital (days)
	Good	Fair	Poor			
50–65	5	3	1	9	0	19
66–75	8	10	5	23	0	19
over 75	6	5	7	18	2	27*
Total	19	18	13	50	2	21

* Excluding the 2 deaths.

Before injection the position of the needle point was proved by negative pressure and loss of resistance, and by aspiration to prevent intravenous or intrathecal injection. (In one of our cases, not in this series, cerebrospinal fluid was obtained at a depth of only 1·5 cm. from an otherwise normal sacral hiatus.) During injection a careful watch was kept for subcutaneous swelling. 15–25 ml. of the lignocaine and adrenaline solution was injected, the amount depending on the size and physical condition of the patient.

Afterwards the patient was placed supine and given a slow intravenous injection of pethidine 50 mg., chlorpromazine 25 mg., and promethazine 25 mg. in water, made up to 10 ml. (The injection may be divided or reduced for very-poor-risk cases.) An intravenous infusion of glucose 5% in water was then started, using a West-Middlesex cannula.

A sleep dose of thiopentone (100–200 mg.) was given, and the patient was well ventilated with oxygen. A large cuffed endotracheal tube could then be inserted easily. If there was any straining on the endotracheal tube after insertion another small dose of thiopentone was given. The 4 patients having endoscopic resections (see below) had no thiopentone. Of the 46 patients who had open operations no thiopentone was given to 5, 100 mg. to 11, 150 mg. to 4, 200 mg. to 8, and 250 mg. to 7. In the remaining 11 patients, because of straining on the tube, the total dosage of thiopentone was more than 250 mg.; in a fit man of 67, the total was 500 mg., this being the largest dose in the series.

Anæsthesia was maintained with nitrous oxide and oxygen, either in a semi-open (Magill) circuit or in a circle absorber. In either case high gas-flows were used.

The nitrous oxide was reinforced by injection of 2–3 ml. of pethidine 50 mg. and chlorpromazine 25 mg. in 10 ml. of sterile distilled water, as required. For muscular relaxation either tubocurarine 7·5–12 mg. (25 cases) or gallamine 40–60 mg. (17 cases) was given after cystoscopy and immediately before the first skin incision, with increments as required during operation. In 1 case tubocurarine 15 mg. was followed by gallamine 30 mg. In the 4 endoscopic resections and 3 open operations no muscle relaxant was required.

During the actual prostatectomy the head was tilted downwards at 5–15°. Respiration was usually assisted, but it was controlled in 14 cases with no apparent effect on pulse, blood-pressure, or recovery.

If indicated by the patient's condition, a blood-transfusion was started during or after enucleation of the prostate. In 6 cases where there was considerable blood-loss it seemed preferable to give a slow postoperative transfusion.

The blood-pressure was carefully charted. It fell considerably from the preoperative level in every case, usually 70–90 mm. Hg systolic. In 15 cases the minimum systolic blood-pressure recorded was less than 70, in 3 it was unrecordable for a short time. During hypotension there was much less blood-loss, and the patient became warm and pink, with a pulse of steady rate and volume, and with good capillary filling.

At the end of the operation the table was levelled by easy stages. In only 1 case, after tubocurarine 10 mg. given about an hour earlier, a considerable degree of curarisation persisted. This was reversed by neostigmine 2 mg. preceded by atropine gr. $^1/_{100}$.

If after the table has been levelled the systolic blood-pressure remained below 80 mm. Hg, a vasopressor was given (usually mephentermine sulphate 15 mg. intravenously with 10–15 mg. intramuscularly if necessary). This was effective in 15 patients, though 1 died later (see below). In 3 cases methamphetamine 10–30 mg. was given, but it seemed less effective than mephentermine. The action of pressor amines on chlorpromazine-induced hypotension is obscure; Foster et al. (1954) found their effect was "inverted", further depressing the blood-pressure, but was not seen in our series.

In 2 cases mephentermine was given to combat excessive persistent hypotension during the actual operation, and in 1 of these a further postoperative dose was required. In this case a total of 45 mg. was given (30 mg. intravenously and 15 mg. intramuscularly) being the largest amount used.

At extubation the mouth and pharynx were gently freed of secretion by mopping. Endotracheal and endopharyngeal suction were employed only if mucus had accumulated, and this was necessary in only 5 cases.

The patient was put back to bed in the operating-theatre, to reduce handling as much as possible. Postoperatively the bed-foot was raised; and only one blanket was permitted, to prevent overheating. An intravenous infusion was continued for 24 hours, and the blood-pressure was carefully checked. Typically, in the 12–18 hours after operation, the blood-pressure rose gradually to about 20–30 mm. Hg below the preoperative level, although in some cases the pressure stabilised at a lower level (i.e., about 100–120). Very little postoperative sedation was required. Postoperative hæmaturia was no commoner than in cases anæsthetised in other ways.

Modification for Endoscopic Resection

Our series included 4 transurethral (endoscopic) prostatectomies, 1 being a local resection of recurrent prostatic carcinoma which had been removed earlier.

In these cases the same technique was employed with the following modifications. No endotracheal tube was inserted, and no thiopentone or muscle relaxant was given. In all except 1 (where nitrous oxide and oxygen were given with a face-mask) no inhalation anæsthetic was used, pure oxygen being substituted.

Modifications for Open Operation

In 2 cases no endotracheal tube was used, and in these and 1 other the lower abdominal wall was infiltrated with 0·1% amethocaine and adrenaline by the surgeon. These cases seemed to follow the same pattern as the others.

Results

The results are summarised in table I and II. There were 46 open operations with 1 death, and 4 endoscopic operations with 1 death, giving a total of 50 consecutive operations with 2 deaths.

Fatal Cases

CASE 14.—A man, aged 81, in fair physical condition, was admitted for endoscopic resection of the prostate. Because of a preoperative urinary infection he had an indwelling urethral catheter. His blood-pressure was 210/90, hæmoglobin 80%, and blood-urea 60 mg. per 100 ml. He had no obvious signs of cardiac decompensation.

Premedication was with pethidine 100 mg. and atropine gr. $^1/_{100}$. Caudal block was performed with 22 ml. of lignocaine 1·5%. Pethidine 35 mg., chlorpromazine 17·5 mg., and promethazine 17·5 mg. were given in three divided doses. Anæsthesia was reinforced with nitrous oxide and oxygen, this being the only case of endoscopic resection where this was done. The minimum blood-pressure recorded was 110/60 about 30 minutes after the start of anæsthesia. At the end of operation, after $1^3/_4$ hours, the blood-pressure was stable at 140/80.

Convalescence was at first normal but on the 5th post-operative day the patient became incontinent and developed signs of a cerebro-vascular accident. Next day he was unconscious; he developed terminal bronchopneumonia, and died on the 8th postoperative day. There was no necropsy.

CASE 16.—A partially blind obese man of 82, classified as of poor physical condition, had 2 weeks earlier developed acute retention, and the bladder had been drained by indwelling urethral catheter. Operation had been postponed because he appeared to be in early congestive cardiac failure, with dyspnœa at rest and sacral œdema. His pulse-rate was 100 per minute and regular, the blood-pressure was 175/100, hæmoglobin 89%, and blood-urea 32 mg. per 100 ml. An electrocardiogram showed probable right ventricular strain. Preoperatively he was treated with digitalis and mercurial diuretics.

Premedication was with pethidine 100 mg. and atropine gr. $^1/_{100}$. Caudal block was performed with 20 ml. of lignocaine 1·5%, oxygen inhalation being administered because of his breathlessness. Pethidine 50 mg., chlorpromazine 25 mg., and promethazine 25 mg. were given, and an endotracheal tube was inserted. Nitrous oxide and oxygen was given from a circle absorber, with assisted respiration. At this stage the blood-pressure had fallen to 110/70, but during the first 30 minutes of the operation it rose to 140/80. During this time he had a total of 15 mg. of tubocurarine in three divided doses, pethidine 15 mg. with chlorpromazine 7·5 mg., and pethidine 10 mg. with chlorpromazine 5 mg. Despite this he seemed to be straining on his endotracheal tube, and thiopentone 100 mg. was given, the blood-pressure then falling during the next 15 minutes to 70/50, and rising in 10 minutes to 80/50 at the end of the operation. Mephentermine 15 mg. was given, and when the patient was sent back to the ward his blood-pressure was 90/50, and his respirations and colour were good.

About 4 hours postoperatively the blood-pressure fell to 60/40, and his condition deteriorated. He never regained full consciousness, and despite large doses of methamphetamine and mephentermine the systolic blood-pressure remained between 40 and 60 mm. Hg. He died 24 hours after operation, and necropsy revealed a massive thrombosis of the left middle cerebral artery.

Summary

Analgesia for prostatectomy (especially for poor-risk cases) by a combination of caudal block with light general anæsthesia has been achieved in 50 consecutive cases with only 2 deaths.

We are indebted to Mr. S. M. Power and Mr. Harold Dodd for their encouragement and help; and to May & Baker Ltd, for their library facilities.

REFERENCES

Baxter, R. W., Bolster, J. A., McKechnie, S. (1954) *Anæsthesia*, **9**, 79.
Courvoisier, S., Fournel, J., Ducrot R., Kolsky, M., Koetschet, P. (1953) *Arch. int. Pharmacodyn.* **92**, 305.
Foster, C. A., O'Mullane, E. J., Gaskell, P., Churchill-Davidson, H. C. (1954) *Lancet*, ii, 614.
Gardner, E. K. (1958) *Anæsthesia*, **13**, 406.
Hopkin, D. A. B., Brown, D. (1958) *ibid.* p. 306.
Whittet, T. D. (1954) *ibid.* **9**, 271.

SIMULTANEOUS CYTOLOGICAL DIAGNOSIS OF CERVICAL CANCER IN THREE SISTERS

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CANCER of the cervix in two sisters, or in mother and daughter, is not unknown. But its simultaneous appearance in three sisters is extremely rare, and in the following three cases the diagnosis was made in each instance by exfoliative cytology.

CASE 1.—A woman, aged 38, consulted one of us (D. C. G.) in 1956 because of backache, but the only abnormality was a mobile retroversion of the uterus. A pessary was prescribed which she wore for 9 months, receiving great relief from her symptoms.

In July, 1958, the patient had a recrudescence of her symptoms. A benign cervical erosion was found and was cauterised after a vaginal smear had been taken. The smear was positive for cervical cancer. In August the cervix had healed, but a

further smear was also positive (J. H. and S. W.). The patient was transferred to the Queen Elizabeth Hospital, Gateshead.

She appeared healthy but had an obvious anxiety neurosis due to worry over an " ailing " husband and a son in trouble with the police. She had been married twice. Her first husband, by whom she had had three children, had been killed in the war. By her present husband she had had one child and two miscarriages. When admitted she was taking gr. $10^1/_2$ per day of various barbiturates on the prescription of a psychiatrist. Her parents were divorced. Her mother had died a year previously, at the age of 55, of diabetes. Her father was alive and well, aged 57; his mother had died at 83 of " uterine " cancer.

On Aug. 23 her hæmoglobin (Hb) was 93%, chest radiographs were negative, and her blood-group was A Rh+. Cone biopsy on Aug. 28 revealed an extensive intraepithelial carcinoma with early stromal invasion. On Sept. 3 a modified radical hysterectomy was performed (S. W.) to remove the uterus, fallopian tubes, ovaries, upper third of the vagina, and inner half of the parametrium.

The cervix was divided into 23 blocks, and two sections were examined from each. Four sections showed residual intraepithelial cancer but no evidence of invasive tumour.

The patient made an uninterrupted recovery and was discharged home on Sept. 13. On Oct. 10, at her first follow-up visit, she was well; a vaginal smear was negative. Since operation she has been weaned from her barbiturates, and now expresses confidence in the future.

CASE 2.—A woman of 37 attended Bishop Auckland Hospital in September, 1958, with persistent bleeding following a miscarriage 11 months previously. She had also had two babies and a miscarriage at 6 months, and had had a retained placenta on each occasion. A vaginal smear was positive, and biopsy of an apparently normal cervix revealed a probable intraepithelial cervical carcinoma. On Oct. 6 she was transferred to the Queen Elizabeth Hospital. She showed a striking resemblance to case 1, and she was indeed a sister.

She had no physical abnormality apart from a recently biopsied cervix and some descent of the vaginal wall. Her Hb was 81%, chest radiography negative, and blood-group O Rh+. A cone biopsy, taken on Oct. 10, showed an intraepithelial carcinoma. On Oct. 15 a vaginal hysterectomy and removal of a cuff of vagina was performed (S. W.). Two areas of residual intraepithelial carcinoma were seen in the operative specimen.

The patient made an excellent recovery and was discharged on Oct. 25.

CASE 3.—The rapid succession of the above two cases prompted us to inquire about further sisters. A third sister, aged 35, was interviewed and asked to submit to cytological examination; she readily agreed.

With a speculum the cervix was seen to be bulky, lacerated, and eroded on the anterior lip. A smear was positive. She was admitted on Oct. 20 into the bed next to her sister. She had no gynæcological symptom; and had had eight normal pregnancies, the first in 1942 and the last in 1956. She did not resemble her other sisters physically, being extremely well built whereas they were both very thin. Her Hb was 105%, chest radiographs were negative, and her blood-group was AB Rh+.

The patient was anxious to have treatment as her husband's sister had died of chest metastases 2 years after an anterior exenteration for a stage-IV carcinoma of the cervix. On Oct. 22, after a cone biopsy, 8 blocks of tissue were examined. All showed intraepithelial carcinoma, and in two sections there was gross stromal invasion. On Oct. 27 a modified radical hysterectomy and appendicectomy was performed, the ovaries being conserved. The cervix was divided into 23 blocks and two sections from each block were examined, but only basal-cell hyperplasia was seen.

The patient was discharged well on Nov. 5, 1958.

Vaginal cytology has slowly but surely proved its value, which is shown once again by these three cases of cervical cancer.

We are indebted to Dr. J. M. Richardson, pathologist to Bishop Auckland General Hospital, for his report on the sections of case 2; to Dr. Denis Fraser and Mr. M. Liggins, assistants in the Gynæcological Research Unit at the Queen Elizabeth Hospital, Gateshead, for their help; and to Mr. George Wilkinson, research assistant in histology, for his invaluable contribution in preparing the histological material. We also wish to thank the British Empire Cancer Campaign, the Royal College of Obstetricians and Gynæcologists, and the Northern Council of the British Empire Cancer Campaign, which have done much to support our work on cytological diagnosis.

Medical Societies

BRITISH ORTHOPÆDIC ASSOCIATION

THE 41st meeting of the Association was held at the Royal College of Surgeons in London on Oct. 22 and 23, with the president, Mr. NORMAN CAPENER, in the chair.

Experimental Investigation of Spinal Injuries

Mr. ROBERT ROAF (Oswestry) described experiments to determine the effect of different forces on fresh specimens of the spinal column. Forces in different planes were applied to the spine and combined with rotational strains. He found that the normal disc was very resistant to trauma, but when the turgor of the nucleus was removed prolapse of the annulus could be produced with comparatively small strains. He found that the vertebral bodies were vulnerable to direct compression. When under pressure the end-plate first of all bulged, then split, and finally the vertebra disintegrated. When the end-plate had split the nucleus pulposus herniated into the body. The mechanism of other spinal injuries was investigated, and he found that the spinal column was vulnerable to comparatively minor horizontal injuries, but not to flexion and extension, and it was shown that dislocations and fracture-dislocations resulted from twisting injuries, particularly if combined with lateral flexion. Twisting injuries of the neck caused separation of the end-plates. He urged that such terms as hyperflexion and hyperextension as applied to spinal injuries should be abandoned.

Mr. E. A. NICOLL (Mansfield) agreed with the mechanisms Mr. Roaf described and pointed out that the facets were fractured four times out of five. He accepted Mr. Roaf's views on the role of rotation in dislocation and said that this knowledge might help in the method of reduction of locked facets.

Mr. JOHN CHARNLEY (Manchester) did not agree that mechanical experiments presented an accurate picture of disc protrusion. Reduction in turgor was not the cause of prolapse but a sequel to it.

Vertebral Clearance for Spinal Tuberculosis

Mr. M. C. WILKINSON (Black Notley) reported the findings in 130 children with Pott's disease for which operation was performed. In children bone destruction was rapid, but it could be reduced by relieving the tension in the paravertebral abscess, and removal of any necrotic bone, but no normal bone should be removed and the end-plates must not be damaged. He advised waiting two to three months before operation because the hyperæmia was less and the disease would to some extent be localised.

He emphasised the importance of early diagnosis and showed some radiographs demonstrating a remarkable degree of restitution of the vertebral bodies after early operation. Bony ankylosis resulted in 82, fibrous ankylosis in 40, and 8 remained unstable. He pointed out the difficulty of being certain that healing was complete without operative exploration, and described the operative approaches to each part of the spine and their merits. Complications had been few: tension pneumothorax on two occasions and hæmorrhage from the fifth lumbar vertebra once (this was controlled by packing).

Mr. DENYS WAINWRIGHT (Newcastle-under-Lyme) had

experienced difficulty in obtaining adequate drainage of paravertebral abscesses, which were often multiloculated, by the usual costotransverse approach. He had found the transpleural approach more satisfactory.

Injuries of Cervical Spine

Mr. R. G. TAYLOR (Oxford) reported a study of 95 injuries of the cervical spine. 51 resulted from hyperflexion and 44 from hyperextension injuries. Hyperflexion injuries accounted for 24 cord lesions, 12 complete; hyperextension for 14 cord lesions, 5 complete. In all 20 patients died, all having cord damage. Only 3 patients with complete lesions survived. The prognosis of cord lesions was bad; more than half died, the majority having complete lesions. The extent of the bony injury gave little indication of the degree of cord damage. In the absence of neurological damage the prognosis was generally good, but late neurological changes, such as brachial neuritis, or even late cord damage, did sometimes develop. Patients who did not die rapidly from the effects of the injury succumbed to intercurrent infection of the respiratory or urinary tracts. Treatment must be directed towards stabilisation and correction of the bony deformity. Residual spasticity was a big problem. Avoidance of excessive stimuli and re-education gave the best results. Antispasmodic drugs were disappointing.

Fracture of Scaphoid

Mr. P. S. LONDON (Birmingham) said that there were two common fallacies in treating fractures of the scaphoid: firstly, that non-union was common; and, secondly, that non-union was a cause of serious disability. He had reviewed 300 fresh fractures of the scaphoid treated at the Birmingham Accident Service. The policy throughout this series had been to treat the wrist rather than the X-rays. Two-thirds of the wrists treated were immobilised for eight weeks or less and only 1 in 10 for more than three months. 5% of fractured scaphoids failed to unite. He had seen a number of fractures in which union was incomplete at two months when the immobilisation was discontinued, but in which sound bony union developed in the next twelve months. Out of 60 ununited fractures investigated from a more extensive series, 56 attended because of a recent strain. Of these, 11 required operation; the remainder were able to return to work after a period of protection. He concluded that only one ununited fracture in a hundred caused serious disability and did not consider that this constituted a sufficiently good reason to justify prolonged immobilisation. Immobilisation beyond three months served no useful purpose.

Prof. B. L. MCFARLAND (Liverpool) agreed that fractures of the scaphoid were often overtreated. Prolonged immobilisation served no useful purpose and often caused a big economic problem.

Mr. NICOLL did not continue immobilisation beyond six weeks because there was no change in the degree of union after that time. If non-union did occur the disability was usually slight. He thought that patients without symptoms had a firm fibrous union, but that a true pseudarthrosis was present in those with pain.

Sir REGINALD WATSON-JONES (London) said that no time limit for immobilisation should be set. The nature of the blood-supply determined the rate of union, and in doubtful cases if immobilisation was continued there would be fewer established non-unions.

Mr. R. H. MAUDSLEY (Ascot) supported Mr. London's view but advocated open reduction and internal fixation with a lag screw when there was displacement of the fragments.

Amputation of All Toes

Mr. M. H. FLINT and Mr. D. R. SWEETNAM (London) described a series of 37 amputations of all the toes, performed on 28 patients with gross deformities. After-treatment included a blocked toe to the shoe and a sponge-rubber insole. The operation had given excellent results and there was no tendency for the longitudinal arch to drop. In a $5^1/_2$-year follow-up, 21 results were excellent, 5 good, and 2 fair. Whoever might claim paternity for this operation there was no doubt that Edward Lear in his rhyme The Popple without any Toes was the first to record the excellent results.

Mr. W. SAYLE-CREER (Salford) had found the operation gave excellent results but he thought it important to trim the metatarsal heads and to suture the flexor and extensor tendons over the end.

Sir REGINALD WATSON-JONES agreed that trimming of the metatarsal heads was an important step and usually did away with the necessity for an insole.

Mr. K. I. NISSEN (London) said the operation gave good results but he had no knowledge of the modifications suggested. He had not found that painful neuromata developed. Follow-up was necessary, particularly in rheumatoid arthritis when there might be a recurrence of cysts.

Tendon Transposition for Paralytic Valgus Foot

Dr. A. AXER (Tel-Aviv) said that in the paralytic valgus foot the talus was unstable because no muscles were attached to it. There was imbalance of the foot due to overaction of the evertors. When the valgus was extreme the head of the talus was unsupported and tilted downwards until it became almost vertical. He described an operation for correction of the deformity. The head of the talus was mobilised and reduced into its correct position. It was maintained in this position by transplanting one or two (but never more than two) of the overacting muscles into the neck of the talus. It was often necessary to lengthen the Achilles tendon to obtain a satisfactory position. Plaster was retained for six months. The results of 26 operations were reviewed. The ages varied between two and nine years, and the time between paralysis and operation from one and a half to seven years. The result was normal in 10, improved in 13, unchanged in 2, and overcorrected in 1. Dorsiflexion was good in 13, limited in 10, and absent in 3. The failures were due to inadequate correction of the talus.

Mr. H. J. SEDDON (London) thought the transplant might be too close to the ankle-joint to provide adequate leverage. He considered that there was a subluxation of the subtalar joint with a tight Achilles tendon. Transplantation of tendons without correcting this subluxation resulted in failure.

Accident Services

A symposium discussed the problem of accident services throughout the country, and was based on the memorandum[1] produced by the British Orthopædic Association.

Discussing the administrative problems involved, Dr. C. T. MAITLAND (London) said that while there were many excellent accident centres it was difficult to provide a good overall standard of treatment, particularly in dispersed rural areas. If life was to be saved there must be a 24-hour service capable of dealing with all contingencies in areas where accidents were most common.. Orthopædics alone could not do this. It was wrong, Dr. Maitland thought, to provide central accident services which were great emporia for the mass treatment of injuries. The centres should be largely for the training of those who must do the bulk of the work at the periphery where more use should be made of the smaller hospitals and even the cottage hospitals.

Discussing some of the legal aspects, Mr. NORMAN SKELHORN, Q.C., said that the legal position of junior medical staff must be considered. Accidents often caused severe and multiple injuries, the diagnosis of which often called for greater experience and more specialised training than a newly qualified house-officer could be expected to have. While all cases could not be treated by senior members of the staff and the difficulties of providing detailed supervision were great, there was at present a tendency to cast upon the recently qualified and comparatively inexperienced doctor more responsibility than he could bear. The law had to hold a balance between the right of the patient to skilled and competent treatment and the legitimate safeguards to which the doctor was entitled. The patient was entitled to expect that those administering the hospital should ensure that there

1. See *Lancet*, 1959, ii, 75, 78.

were available, proper qualified staff of reasonable competence and that there should be available facilities and equipment for his treatment in accordance with recognised standards. From the doctors he was entitled to receive the care and skill of the ordinary medical practitioner—no more and no less. It was no defence to a charge of negligence that the particular house-officer was insufficiently experienced to perform his or her duties.

It was true that the practitioner had to learn his job largely by experience. But it was necessary that this experience should not be gained at the expense of the proper and skilled diagnosis and treatment to which the patient was entitled. Adequate supervision must be assured. The competent practitioner must know when a case was beyond his skill and it then became his duty to call in a more skilled person, or to order the removal of the patient to a hospital where that special skill was available. It was of great importance in the interests of the profession and, in the long view, of the public, that surgeons and doctors should be able to make decisions boldly, without fear of the spectre of litigation. Mr. Skelhorn considered that the proposals in the British Orthopædic Association's memorandum went far to solve many of these problems.

There was considerable feeling in the medical profession that free legal aid had increased the number of unjustifiable claims made. The legal aid committees could only decide on the facts before them whether or not a case had a chance of success. No case could succeed in court unless the plaintiff's claim was supported by some member of the medical profession. It was greatly to the credit of the medical profession that eminent doctors or surgeons were prepared fearlessly to support proper claims and to expose negligence, and it would be a sorry day for the profession and the public when this ceased to be so.

Mr. LIPMANN KESSEL (London) said that road accidents had become the endemic disease of this generation. Last year 6000 people were killed, and 70,000 seriously injured. In Great Britain 45 people were killed each day, 24 in the home, 16 in travel, and 5 in their place of work. Prevention of accidents involved central Government policy, but orthopædic surgeons had a special responsibility in providing a medical service for the victims. There were three main problems: the casualty departments, dissemination of casualties among many hospitals, and specialist responsibility for treatment. A series of articles in *The Lancet* three years ago pointed out the generally low standard in casualty departments, which was the greatest weakness of the hospital service and was responsible for much unnecessary suffering and great economic loss. The memorandum stated that "a fundamental defect of the present system was the diffusion of injured patients among hundreds of hospitals". This defect was particularly serious in big centres, such as London, where the reception of casualties was disseminated among a hundred or more hospitals. It would be wiser to have fewer well-equipped centres which could provide a thoroughly efficient 24-hour service. Although most patients attending accident departments were an orthopædic responsibility, Mr. Kessel did not feel that orthopædic surgeons should automatically be leaders of the teams. There should be centralised control, but the leader should be the person most suitable at the time, whatever his specialty.

Why should orthopædic surgeons have to work in 19th-century conditions, and why should the public accept casualty services often fifty years out of date? In Lowden's words[2]: "we may not be able to afford it, but can we afford *not* to have it?"

Mobilisation of the Stiff Knee

Dr. ROBERT JUDET (Paris) described an operation which, since 1953, he had carried out on 70 occasions for mobilisation of a stiff knee. The operation was performed only when there was no further possibility of spontaneous improvement. The patella and suprapatellar pouch were mobilised through a medial parapatellar incision which must be at least 1 in. away from the patella. Through a 10-in. incision on the postero-lateral aspect of the thigh the vastus lateralis and intermedius were separated from the shaft of the femur in their entirety. Sometimes it was necessary to mobilise the vastus medialis as well through a medial incision. Intensive rehabilitation followed from the day of operation. Of 53 operations, 44 were for fracture of the shaft of the femur, 5 for fracture of the lower end, and 4 for arthritis. The results were excellent (100° or more) in 24, good (80°–100°) in 21, fair (50°–80°) in 6, and bad (less than 50°) in 2. Complications were few.

Mr. I. MCQUEEN (Bristol) emphasised the importance of rehabilitation after such an operation and said it was important to concentrate on the adductors and hamstrings as well as the quadriceps.

Mr. J. N. WILSON (London) preferred the less radical operation described by Thompson, which he thought gave comparable results. It had the advantages of allowing release of the tensor fascia lata at the knee and also avoided a potentially infected area if the fracture had been compound.

Flexion Contracture of the Knee

Mr. E. W. SOMERVILLE (Oxford) said there were two types of flexion contracture of the knee. The simple type in which, when the posterior contracted structures were stretched or divided, the tibia glided round the femoral condyles into extension; and the type in which, when the contracted structures were stretched or divided behind the knee, the tibia hinged on the femur instead of gliding. This could be explained by studying the functional anatomy of the knee-joint. The attachment of the lateral and anterior cruciate ligaments was so arranged that when the knee was in extension they were tight, and when the knee was flexed they were relaxed. If a flexion contracture has been present for a long period the anterior cruciate ligament may have undergone adaptive shortening so that the joint extended by hinging instead of gliding. If it proved impossible by simple means to correct this it was logical to cut the anterior cruciate ligament. Examples were shown in which this had been done successfully to flexion contractures due to trauma and rheumatoid arthritis.

The Patello-femoral Joint

Mr. P. R. FRENCH (London) described the mechanics of the patello-femoral joint. During weightbearing the joint took an increasing strain the more it was flexed. At 90° of flexion the pressure was equal to twenty times the body-weight. Osteoarthritis was accepted as being a mechanical disorder resulting from some incongruity of the joint surfaces. In the knee osteoarthritis usually began in the patello-femoral joint. Recurrent dislocation of the patella caused the most rapid wear, and subluxation rather less. Chondromalacia was an early stage of osteoarthritis, as was fibrocartilaginous proliferation of the surface of the patella. Osteochondritis dissecans of the medial femoral condyle resulted from impact of the patella against this area when the knee was bent. Many loose bodies in the knee were cartilaginous and invisible on X-ray; these often arose from the patella. Any knee with episodes of pain and recurrent swelling should be explored with a view to patellectomy, which gave good results. Out of 55 reviewed, 40 were good, 10 fair, and 5 poor. The poor results were usually due to the operation being done too late.

Subacute Arthritis of the Sternoclavicular Joint

Mr. R. A. BREMNER (York) described a condition of unilateral swelling of the sternoclavicular joint. He reported this in 12 patients, all women between the ages of 34 and 63. The joint was neither tender nor warm and no other joint was involved. In some the radiographs suggested a little erosion of the clavicle. In 11 the lesion was on the right and the patients were right-handed, and in the other one on the left, the patient being left-handed. 7 were treated by exploration and 5 were untreated. Biopsy showed a non-specific synovitis. Those untreated ran a constant course. The swelling slowly regressed for nine to twelve months, leaving only a little thickening. There was no evidence that this condition was related to rheumatoid arthritis and the prognosis without treatment was excellent.

2. Lowden, T. G. *ibid.* 1956, i, 1006.

Reviews of Books

Epidemic Diseases

A. H. GALE, D.M., D.P.H., late director of postgraduate medical studies, University of Bristol. Harmondsworth: Penguin Books. 1959. Pp. 159. 3*s.* 6*d.*

THE writing of history is bound to be plagiarism with or without acknowledgments, and it is lamentably true that most authors who write on the history of infectious disease quote the same stories and reach the same conclusions. For this reason the chief virtue of the late Dr. Gale's book is its novelty. One would think that after Crawford and Greenwood there was little fresh to be written about plague, but this account covers new and rewarding ground and includes what is to the best of our knowledge the only account of the Suffolk outbreak in 1909–11 outside a bluebook. Every chapter gives evidence of an inquiring and scholarly mind, and the last (on the relative importance of different diseases at different times) will be of value to many historians. This excellent book is simply written and is as suitable for that mythical intelligent layman as for a medical student. We hope that it will be reprinted in a more permanent form.

Malariology

With Special Reference to Malaya. A. A. SANDOSHAM, L.M.S., PH.D., professor of parasitology, University of Malaya, Singapore. Singapore: University of Malaya Press. London: Oxford University Press. 1959. Pp. 327. 35*s.*

THIS book has clearly been written by an enthusiastic teacher who not unreasonably considers that "the textbook still remains the mainstay of the serious student". There is at present, he remarks, no teaching manual which provides the student of malariology in Malaya with the material he needs; and this is an attempt to provide it. Its contents are directed both to undergraduate medical students and to postgraduates taking the diploma in public health at the University of Malaya, so the earlier part contains more elementary information than the later chapters. Throughout the writing is clear and direct, and the material well arranged (with liberal use of bold-faced type), up to date and accurate. Teaching is oriented towards control and prevention, so that clinical features of malaria and its treatment are dealt with only in so far as they are concerned with these aspects. In debatable matters (for example, in the choice of methods of malaria control and the relative merits of the different chemoprophylactic agents) the differing viewpoints are fairly presented. Though particularly welcome to students in Malaya, Professor Sandosham's book will also interest those concerned in malaria prevention in all parts of the world.

Intravascular Catheterization

Editor: HENRY A. ZIMMERMAN, M.D., chief of the cardiovascular section, Division of Medicine, and director of the Marie L. Coakley Cardiovascular Laboratory, St. Vincent Charity Hospital, Cleveland, Ohio. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959. Pp. 782. 126*s.*

Dr. Zimmerman's object was to provide "a comprehensive text on the entire field of cardiac catheterization". To achieve it, he invited 22 American workers, many of them internationally famous, to contribute articles on particular aspects to which they had made special contributions.

There can be no denying the comprehensiveness of the book, which includes articles on the techniques of catheterisation of the coronary sinus, hepatic veins, and renal veins, in addition to the more straightforward right and left heart catheterisation. There are also accounts of pressure-curve analysis, shunt flows, and valve areas, and the application of the various procedures to congenital and acquired heart-disease. Other articles are concerned with the hæmodynamics of the pulmonary circulation, intracavity electrocardiography, indicator dilution curves, selective angiocardiography, and the technique of unilateral pulmonary artery occlusion. There is nothing about the technique of left ventricular puncture and the results obtained by it.

Each author has given his personal opinion in a style of his own, and this seems to have been deliberate editorial policy; but it has led to unusual variations in style and to considerable repetition. Some articles, notably those on left heart catheterisation (D. L. Fisher) and the application of cardiac catheterisation to cyanotic congenital heart-disease (Dr. S. Gilbert Blount), are well documented, pleasing to read, and highly informative. Others concentrate more on personal experience, so that they do not so adequately cover their subject. Dr. Zimmerman's own article, for example, on the technique of right heart catheterisation is confined to the detailed technique imposed by the equipment available in his laboratory, and, in many respects, would not be applicable to the same procedure performed with different equipment.

This well-produced and lavishly illustrated book usefully provides in one volume an account of the many aspects of intravascular catheterisation. At the present rate of progress a second edition will probably be called for quite soon, and that might be an opportunity to introduce a stricter editorial policy to avoid repetition.

British Obstetric and Gynæcological Practice: Obstetrics (2nd ed. London: Heinemann. 1959. Pp. 1228. 147*s.*).—The second edition of the volume in obstetrics, edited by Sir Eardley Holland, appears four years after the first. The minor discrepancies inevitable in the first edition of a composite work have nearly all been adjusted. Two excellent new chapters have been added, on the functions of the placenta and the adaptation of the fœtus from intrauterine to extrauterine life. All the other chapters have been revised, and considerable changes have often been made in bringing them up to date. Our review of the first edition suggested that, especially for overseas readers, a book on British practice should include a description of the organisation of maternity services in Britain. Sir Eardley himself has now contributed an excellent account of present arrangements. One of our other suggestions—namely, that the illustrations depicting the palpation of the fœtus in utero be not borrowed from an American textbook—has not had such a happy result. New drawings have certainly been substituted but their quality falls far below the very excellent general standard of the rest of the illustrations. The reproductions of X-rays are improved beyond all measure and are now first-class. The publishers are to be congratulated on the improved quality of paper and on the production generally. This two-volume work has now established itself as an important contribution to the specialty.

"Allergic" Encephalomyelitis (Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959. Pp. 576. 102*s.* 6*d.*).—On Oct. 19 and 20, 1957, 59 people gathered at the National Institutes of Health, Bethesda, to discuss nineteen papers on allergic encephalomyelitis. Special attention was given to the immunological mechanisms concerned and to the problem of identifying the encephalitogenic agent. This volume, ably edited by Dr. Marian W. Kies and Dr. Ellsworth C. Alvord, contains much valuable material for the specialist. For the general neurologist there is a useful discussion on the inter-relationships of demyelinating diseases.

Lectures on the Scientific Basis of Medicine (*Vol. VII.* London: University of London, The Athlone Press. 1959. Pp. 496. 45*s.*).—The British Postgraduate Medical Federation's popular annual series of lectures is again attractively recorded. These are lectures given in 1957–58 and all but seven of the thirty have been published. Many of them reflect the intense interest and activity now apparent in cellular biochemistry.

Eat Well and Stay Well, by Ancel and Margaret Keys (see *Lancet*, Nov. 7, p. 773), is to be published next year in this country by Hodder & Stoughton at 15*s.*, with the section on menus and recipes edited by Dr. Magnus Pyke to bring them into line with British tastes.

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THE LANCET

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The Nature of Essential Hypertension

IT is nearly sixty-five years since ALLBUTT recognised that high blood-pressure often occurred in the absence of renal disease. Yet the causation and mechanism of "essential" hypertension still remain a mystery. There is evidence that inheritance, psychological stress, hormonal and electrolyte disturbances, and renal ischæmia may be contributory factors, but their relative roles have still to be determined.

Is there a discoverable pattern of genetic and environmental causes which produces a disease entity in certain individuals, distinguishing them qualitatively from the rest of the population, or is high blood-pressure (without evident cause) one extreme of a characteristic graded throughout the whole community like height or intelligence? This latter concept was put forward by PICKERING and his colleagues [1] as a result of blood-pressure studies on hospital outpatients and their relatives. They found that blood-pressure conformed to "continuous" or unimodal frequency-distribution curves at different ages. These curves differed from "normal" in showing a prominent tail to the right (positive skewness); but no evidence was found of a double peak (bimodality) such as might be expected if the population contained a hypertensive group of individuals differing qualitatively from the remainder. It was concluded that there is no natural dividing-line between those with high blood-pressure and those without, and that "essential hypertension represents not a disease entity, but merely that section of the population presenting arterial pressures higher than an arbitrarily selected value". This concept is valid only if the apparently continuous distribution-curve does in fact indicate a homogeneous population. The alternative is that the "continuous" curve is a resultant of two or more curves, and that one of these may represent a subgroup of the population qualitatively different from the rest. Recently PLATT [2] suggested a method for unmasking such a subgroup. From the data of PICKERING and his coworkers, and from similar data previously recorded by SOBYE,[3] he plotted the blood-pressure frequency-distribution in siblings, aged 45–60, of hypertensives in the same age-group. By this procedure he obtained bimodal curves among the siblings for both systolic and diastolic pressures. This segregation of siblings into two distinct groups—one with hypertension and one without—strongly suggests that essential hypertension is a definite entity.

On an earlier page of this issue Dr. MORRISON and Professor MORRIS describe observations which confirm and amplify this interpretation, bringing us back once more to the classic view. On the question of continuous distribution curves with positive skewness, they refer to the work of HARRIS and SMITH [4] which showed that a combination of two populations can produce either a bimodal or a unimodal "continuous" curve depending on the relative sizes of the populations and other factors. In their studies on cardiovascular disease in London busmen, MORRIS and his colleagues obtained data on the ages of the parents at death. Since hypertension is an important factor in shortening the expectation of life, death in middle age might be expected to be associated with hypertension much more commonly than death in old age. MORRISON and MORRIS therefore compared blood-pressure distribution in two groups of busmen—those whose parents had died in middle age, and those with parents living to old age. The former group clearly showed a bimodal distribution, while the latter did not. Thus by using the inheritance factor it was possible to separate busmen into clear-cut hypertensive and non-hypertensive groups. The blood-pressure level separating these groups, which may well indicate the change from normal pressure to hypertension, was approximately 160/95 mm. Hg. This is close to the figure obtained by PLATT from his analysis of data obtained by two independent observers; and the W.H.O. Expert Committee on Cardiovascular Diseases has on different grounds accepted this level as the lower limit of hypertension.[5]

By a similar technique the effect of age on blood-pressure levels was compared in these two groups of busmen. It was discovered, first, that the increase of average blood-pressure with age in the total population studied was due to the emergence in older age-groups of an increasing number of individuals with high blood-pressure, and, second, that this increase was confined to the busmen whose parents had died in middle age. These findings support the view put forward by ROBINSON and BRUCER [6] and PLATT [2] that the rise in pressure with age is confined to hypertensive subjects; they do not support the contention of PICKERING [7] that there is a general tendency for blood-pressure to rise with age. This clarification of the influence of age on the blood-pressure level further strengthens the case for regarding hypertension as a disease entity, rather than a physiological variation.

The nature of the genetic factor is still disputed. HAMILTON et al.[1] and more recently MIALL and OLDHAM [8] concluded, from the "continuous" nature of the blood-pressure distribution curves in representative populations, that inheritance was multifactorial. HAMILTON et al. introduced "age and sex adjusted scores" in order to compare blood-pressure levels in relatives of different ages and sex. They found a regression of 0·2 between the pressures of first-degree relatives and hypertensive subjects, and a similar regression coefficient was found by MIALL and OLDHAM to apply at *all* levels of blood-

1. Hamilton, M., Pickering, G. W., Roberts, J. A. F., Sowry, G. S. C. *Clin. Sci.* 1954, **13**, 11, 37, 273.
2. Platt, R. *Lancet*, July 25, 1959, p. 55.
3. Sobye, P. Heredity in Essential Hypertension and Nephrosclerosis. Copenhagen, 1948.
4. Harris, H., Smith, C. A. B. *Ann. Eugen.* 1949, **14**, 309.
5. *Tech. Rep. Ser. Wld Hlth Org.* 1959, 168.
6. Robinson, S. C., Brucer, M. *Arch. intern. Med.* 1939, **64**, 409.
7. Pickering, G. W. High Blood Pressure. London, 1955.
8. Miall, W. E., Oldham, P. D. *Acta genet.* 1957, **7**, 114.

pressure. It was concluded that arterial pressure was transmitted as a graded characteristic, hence that inheritance was multifactorial. PLATT,[9] on the other hand, from the observed frequency of a positive family history in subjects with essential hypertension, had postulated that inheritance was due to a single gene, behaving as a mendelian dominant. As we have seen, his re-examination of the figures for middle-aged subjects supported this hypothesis and exposed the fallacy of using scores " adjusted " for age and sex. Pursuing this line of argument, MORRISON and MORRIS compared the ages at death of the fathers of hypertensive and normotensive busmen. Their analysis showed a clearly bimodal distribution for fathers of busmen with hypertension, but not of those with normal blood-pressure—an observation which strongly suggests inheritance by a single dominant gene.

In bus-drivers on the one hand, and conductors on the other, the proportion of parents who had died in middle age was the same, from which it was inferred that men in the two occupations had essentially similar genetic loading for hypertension. Nevertheless, the frequency of hypertension among men whose parents had died in middle age was dissimilar—34% in drivers and 18% in conductors. Apparently, therefore, environmental factors connected with occupation (or choice of occupation) may either enhance (or diminish) the genetic effect.

We find this new evidence that essential hypertension is a specific disease both convincing and more in keeping with its clinical behaviour. The epidemiological method is being increasingly and profitably brought to bear on problems of chronic disease in which ætiology is obscure. The interpretation of population statistics is obviously fraught with risks of error when the behaviour of subgroups is masked by variation in the population as a whole, so that the possibility of their existence is overlooked. There is clearly much work ahead for the epidemiologist in mapping out the experiences of different population groups, and in following the behaviour of large numbers of individuals before and during middle age. For the clinician there is promise of a more meaningful diagnosis: definite distinction between normal and high blood-pressure may at last be in sight. The relation of casual readings of high blood-pressure to essential hypertension needs further study: the finding of a high casual blood-pressure in a patient with a positive family history apparently justifies the diagnosis of this disease—at any rate in the sex and age groups studied by MORRISON and MORRIS. For the investigator there is renewed assurance that search for the cause of essential hypertension is still justifiable, and indeed more necessary than ever since a bimodal distribution points to some specific cause. If inheritance is by a single gene this possibility is reinforced, and we might think in terms of some metabolic defect, hormonal or enzymatic. Environmental factors would in that event seem to be contributory rather than determining causes, possibly exerting their influence on the natural history of the disease in its various stages. This new contribution by epidemiologists is important, not only for its content, but as a fresh stimulus for a vigorous and many-sided inquiry into the nature of essential hypertension.

9. Platt, R. *Quart. J. Med.* 1947, **16**, 111.

Mass Treatment of Tuberculosis

IN Britain and other of the more favoured countries there are too many sanatorium beds: in India and many other countries there are too few. India is estimated to have $2^1/_2$ million people with active tuberculosis requiring treatment but only 23,000 tuberculosis beds for them—100 patients per bed. There, as elsewhere, if the tuberculous are to be treated at all they must be treated in their homes; but even this is impossible on a large scale in some countries, where neither the patient nor the State can pay for drugs and medical and nursing care. A few years ago no-one knew whether chemotherapy in the home was as effective as treatment in a sanatorium; and the traditional idea of the value—even the necessity—of sanatorium treatment was still deep-rooted and widespread. It was surmised that mass treatment in the patients' homes might lead to a serious public-health hazard from an increasing number of chronically infectious " failures " excreting resistant tubercle bacilli; and some thought that it would be premature to begin mass home chemotherapy, even in a limited area. In these circumstances the Government of India decided to undertake controlled comparative studies of home and sanatorium treatment and supervision of the patients' contacts.

In 1956 the Tuberculosis Chemotherapy Centre was set up in Madras under the joint auspices of the Indian Council of Medical Research, the Madras State Government, the World Health Organisation, and the Medical Research Council of Great Britain. After a series of pilot investigations the first study began in September, 1956; and the first substantial report has now been published.[1]

Patients were selected for the study from those attending local chest clinics in Madras city and living in a defined area with a population of about 750,000. Most of them were from the poorest section of the community. They had to fulfil certain criteria, the main ones being that they had not had more than two weeks' chemotherapy in the past, had tubercle bacilli in the sputum, were prepared to accept treatment at home or in sanatorium for at least a year and would permit home visiting, and had cooperative families. The staff of the centre was large: doctors, bacteriologists, health visitors, social workers, radiographers, laboratory and clerical staff, statisticians, and a dietitian. The patients were randomly allocated to one of two groups. All received the same chemotherapy—cachets containing isoniazid and the sodium salt of *p*-aminosalicylic acid (P.A.S.), in two doses a day, the total daily dose for patients weighing 100 lb. or more being 200 mg. isoniazid and 10 g. sodium P.A.S. This was continued for twelve months. One group of patients was admitted to the Government Tuberculosis Sanatorium, Tambaram; the other was treated at home. Patients at home attended the centre weekly throughout the whole period, if well enough; if not, they were brought by ambulance at longer intervals. A health visitor went to each home once a week for the first month and at least

1. Tuberculosis Chemotherapy Centre, Madras. *Bull. Wld Hlth Org.* 1959, **21**, 51.

twice a month for the remaining eleven months. Intensive sputum examinations were carried out, with culture and sensitivity tests, at least two cultures being set up from sputum or laryngeal swabs each month.

Altogether 193 patients were admitted to the study, but for various reasons 30 could not be included in the main analysis. This concerned, therefore, 163 patients—82 treated at home and 81 in sanatorium. Despite strict attention to random allocation there were, unfortunately, important differences in the pre-treatment state between the home and sanatorium patients: those treated at home had more severe disease, the difference being greater among women than men. Direct comparisons of the results of treatment have, therefore, to be interpreted cautiously. A special analysis was undertaken, with statistical standardisation applied to the various measures of progress, to assess the influence of the pre-treatment differences. This had the effect of reducing the small differences between home and sanatorium groups among the men and the larger ones among the women in regard to radiographic change; but standardisation did not reduce the considerable differences among the women in bacteriological changes.

Comparison of the 49 males at home with the 50 in sanatorium showed that those in sanatorium had gained more weight and that the decrease in their erythrocyte-sedimentation rate was greater. On the other hand, the two series had fared almost equally well in radiographic improvement, including cavity closure, and in bacteriological response. The standardised comparisons between the 33 females at home and 31 in sanatorium suggested that both series had similar radiographic improvement, but that the females at home had had much less good bacteriological results. In the whole series of patients treated at home the proportion with positive cultures (one specimen monthly) fell rapidly to 32% at three months and 11% at twelve months; in those treated in sanatorium the corresponding figures were 21% and 8%. Of 153 patients treated in or out of hospital 13 (8%) had a positive culture after twelve months' chemotherapy: 80% had "quiescent" disease at the end of the year. There seem to be good grounds for the conclusion that the results of chemotherapy at home, as practised in this study, "approach sufficiently closely the results of sanatorium treatment to suggest that it is appropriate to treat the majority of patients at home". But, despite the careful wording of the report, there is some danger that the conclusions may be misinterpreted and similar results of home treatment be expected under any conditions in any country, merely by distributing the drugs. The report emphasises that certain minimum requirements must be fulfilled: among these are adequate supplies of drugs, enough staff (including public-health nurses and social workers), efficient clinic organisation, reliable smear examinations of sputum, and a welfare fund for specially needy patients. Even with these essentials the efficacy of home chemotherapy may be found to vary from clinic to clinic and country to country, under the influence of such factors as the enthusiasm of the staff and the cooperation of the patients. The Madras study concerned only patients judged before treatment to be cooperative and likely to remain for several years in the same locality. It is not stated what proportion of patients were found unacceptable for study; but, however good the clinic staff and facilities, the results of home treatment with cachets of P.A.S. and isoniazid might be considerably less favourable than in the Madras study if all tuberculous patients were to receive it. Yet the results in this study, though promising—particularly in the rapid decrease of infectivity—should certainly not be accepted as the best attainable. Isoniazid-resistant cultures appeared in 27 patients, though only 16 were thought to have been a source of danger to the public health. In countries where it is economically possible to use streptomycin freely and to admit patients to hospital at will, such a proportion of failures would be unacceptable. CROFTON [2] in Edinburgh, for instance, reported that each of 240 patients with initially sensitive bacilli became sputum-negative within a year; and in the U.S.A. RUSSELL et al.[3] reported similar results in all but 1 of 153 patients. Even patients with extensive lesions and large cavities can almost always be made non-infectious by chemotherapy, provided the pre-treatment cultures are sensitive to the drugs used and the regimen includes streptomycin and isoniazid daily in at least the first phase of the treatment.

Large clinical trials have been rightly concerned with the effects of certain uniform regimens for all patients; but probably not every type and severity of disease requires the same treatment: with a uniform regimen some may get too much and others too little. If drugs and money could be saved in the less severely ill, the more severely ill might be treated with more powerful combinations than P.A.S. and isoniazid in the doses used in the Madras study. There may be a case for investigating, by the precise methods that have been applied to fixed regimens, drug treatments that are varied, within defined limits, with the characteristics of the individual patient's disease. Other aspects of mass treatment need further investigation. In the Madras study, for instance, many patients at home failed to take the drugs regularly (though there was no clear evidence that those who fared badly had taken the drugs less regularly than those who fared well). This difficulty of regular self-medication is becoming well recognised; but further inquiry is required to establish how frequently the drugs need be taken in the later stages of treatment, and how best, under different social circumstances, the patients can be persuaded to take them in the prescribed dosage. A method of distribution suitable in an English city may be quite unsuitable in remote rural districts of Ghana or Brazil; uncritically to impose in one country a technique found satisfactory in another may be unrewarding or even wasteful. Where the number of patients that can be treated is strictly limited by the amount of money that can be spent on the drugs, expensive cachets, tablets, or powders should not find their way on to refuse heaps. Nor is it desirable that distribution of the drugs should be in unauthorised

2. Crofton, J. W. *Brit. med. J.* 1959, i, 1610.
3. Russell, W. F., Kass, I., Heaton, A. D., Dressler, S. H., Middlebrook, G. *J. clin. Invest.* 1959, **38**, 1366.

hands, for inadequate chemotherapy by unskilled people or by unrestricted purchase and self-administration will almost certainly increase the risks of infection by resistant organisms and reduce the benefit from mass-treatment schemes, with further economic loss.

The poorer countries will be considerably aided by the knowledge that is being accumulated by purposeful clinical trials, such as the Madras project. More such experiments are necessary; and the more favoured Western countries, with their money and technical skills, could offer more help than they have provided so far.

Surgical Treatment of Mitral Stenosis

THE first operations on the mitral valve were those devised by CUTLER and LEVINE [1] and SOUTTAR [2] in the 1920s, and from then on progress has been remarkable, particularly since the modern procedure was introduced.[3–5] It soon became clear that the most satisfactory approach to the mitral valve was by means of a finger introduced through the left atrial appendage, and for the first few years all valvotomies were done by the surgeon's finger in this way. But although the left atrial route is best for palpating the valve and determining its condition, the results of finger-fracture alone were often unsatisfactory, because the commissures could not be completely divided. So the next development was a cutting instrument introduced via the left atrium and guided into position by the surgeon's finger. The fused valve cusps could then be divided more effectively, but it was often very hard to identify the exact site of the commissure, and a knife cut in the wrong place might well lead to disorganised valve function and serious incompetence. DUBOST [6] therefore introduced mechanical splitting of the valve by a transatrial dilator, which had the advantage over the finger that no counter pressure from outside was needed to split a resistant valve, and its action was the same as the finger's in that it stretched the valve until it gave at its weakest point, which was usually where the commissures were fused. Mr. LOGAN and Dr. TURNER, whose paper we publish this week, were dissatisfied with the atrial approach but impressed by the possibilities of the mechanical dilator; and in 1954 they began to use a transventricular dilator, guided into position by a finger in the left atrium. They review (p. 874) 438 patients who have undergone mitral valvotomy performed with the transventricular dilator. Since LOGAN introduced this technique, it has been widely used by surgeons in this country and abroad; but this is the first large series described by the originators of the method, and an account of their experience has been awaited with keen interest by cardiac surgeons. This issue also includes a report by Mr. CRUM and Dr. TSAPOGAS of 50 consecutive mitral valvotomies performed in this way.

1. Cutler, E. C., Levine, S. A. *Bost. med. surg. J.* 1923, **188**, 1023.
2. Souttar, H. S. *Brit. med. J.* 1925, ii, 603.
3. Bailey, C. P. *Dis. Chest.* 1949, **15**, 377.
4. Harken, D. E., Ellis, L. B., Ware, P. F., Norman, L. P. *New Engl. J. Med.* 1948, **239**, 801.
5. Baker, C., Brock, R. C., Campbell, M. *Brit. med. J.* 1950, i, 1283.
6. Dubost, C. *Pr. méd.* 1954, **62**, 253.

The most important finding was that the valvotomy was much more thorough with the dilator, and the proportion of cases in which division of both commissures was incomplete dropped from 26% to 11%. This should mean that re-stenosis of the valve will be considerably less common after transventricular dilation. As experience grew the dilator was used in more and more operations until it became the routine in almost every case. Valvotomy by the finger in the atrium was always tried first, but these preliminary attempts became more gentle as the series progressed. When there was clot in the atrium the dilator technique had a positive advantage in that manipulation of the valve could very often be much reduced, and the finger had to be inserted only once, thus decreasing the risk of liberating emboli. The instrument should have stops on it so that the maximum opening can be varied (most surgeons choose a maximum between 3·5 and 5 cm.) and the ideal spread was provided by the instrument designed by O. S. TUBBS.

A criticism levelled against this technique is that it increases the risk of traumatic mitral incompetence, but in LOGAN and TURNER's series there have been only 6 deaths from this cause out of 438 operations, as opposed to 4 deaths out of 388 in the pre-dilator series. LOGAN emphasises that a suitable mechanical stop on the dilator and steady dilation to avoid sudden rupture of the valve are important in avoiding traumatic incompetence. If the dilator completely divides one commissure and not the other, it is dangerous to dilate further because that could lead to rupture of the mitral ring with gross incompetence. Calcification of the valve is not a bar to the use of the instrument. LOGAN says that the exact position of the dilator in relation to the valve at the time of opening is unimportant since the valve will always split at its weakest point—namely, along the commissures. But CRUM and TSAPOGAS aimed to open the instrument in the line of the commissure. It seems reasonable to exert if possible the greatest pressure on the weakest point—where the commissures are fused—but if this cannot be accurately identified it is valuable to know that no harm will be done by deviating from this line.

The mortality-rate in LOGAN and TURNER's series is slightly higher (6·4%, compared with 5% in their pre-dilator series), but against this must be balanced a considerably more efficient opening of the valve by the new technique. Calcification of the valve was not associated with a higher mortality; and figures for cerebral embolism were slightly lower. Moreover, ventricular fibrillation was not apparently a problem. The transventricular technique has shown itself to be one of the major advances in mitral surgery in recent years. The same results can be and are obtained by other operations with finger-knives or guillotines, but LOGAN's method is the easiest to perform and probably the safest. The results of blind operations will hardly improve on the transventricular figures, and this operation is likely to remain the standard approach to mitral stenosis in this country for some time.

Annotations

SUBARACHNOID HÆMORRHAGE AND CEREBRAL INFARCTION

SUBARACHNOID hæmorrhage results, in more than 80% of cases, from the rupture of an intracranial aneurysm [1–3]; bleeding from an arteriovenous angioma is another common cause. In as many as half the cases "subarachnoid hæmorrhage" is a misnomer, for the hæmorrhage encroaches on the cerebral substance as well as the subarachnoid space, [2 4] and bleeding into the subdural space occurs in up to 5% of cases.[5] When a patient presents with the typical clinical picture of subarachnoid hæmorrhage, and then develops neurological symptoms or signs such as aphasia or paralysis of one or more limbs, it is commonly assumed that these must be the direct result of bleeding into or over the surface of the brain. Comparatively little attention has been paid to the fact that cerebral infarction is a common and important complication of bleeding from an intracranial aneurysm.

As Tomlinson [6] points out, this omission has probably been due to the fact that the brains of patients who have died as a result of aneurysmal rupture have not often been examined carefully for the presence or absence of ischæmic lesions. Robertson [4] found that infarcts were mentioned in only 2 out of 80 cases in which he reviewed the necropsy findings, while infarcts were discovered in 3 of the 10 cases which he studied personally. In 1954 Wilson et al.[7] found ischæmic lesions in 45% of their cases in which death was due to bleeding intracranial aneurysm. Now Tomlinson,[6] reporting a personal study of 32 consecutive fatal cases, has discovered massive cerebral infarction in 13 (40%). Indeed he suggests that infarction, rather than intracerebral hæmorrhage, may be the predominant cause of residual disability in patients who survive but show signs of focal brain injury. Tomlinson points out that in his cases the infarcts were sometimes multiple; sometimes they lay in the distribution of the artery on which the bleeding aneurysm lay, but this was not always so. Thrombotic occlusion of a major artery was not observed in any case, and in the great majority there was no evidence that cerebral angiography, surgical interference, or any other form of treatment could have been responsible for, or related to, the development of the infarct. From the evidence he presents, Tomlinson is not prepared to draw firm conclusions about the ætiology of the infarction in these cases.

In some cases it may be due to pressure on the parent vessel by a localised collection of blood, and in others to tearing of perforating branches of the artery at the time of the hæmorrhage. Localised collections of blood between the frontal lobes or in the Sylvian fissure seem to be particularly common and may compress the anterior or middle cerebral arteries. There is also, however, a good deal of experimental evidence that arterial spasm, which may follow trauma to the cerebral vessels (such as is produced by hæmorrhage around them), is probably an important ætiological factor. Widespread arterial constriction seems to be common in the first four or five days after hæmorrhage.

These findings have important therapeutic implications. Clearly hypotensive therapy designed to reduce bleeding may promote infarction by lowering the blood-flow through arteries which are already narrowed, while operative treatment carried out too soon may increase the liability to infarction by further damaging the vessels. On the other hand, it is clearly important to evacuate as early as possible a localised hæmatoma which is capable of compressing major arteries. Fortunately evidence is accumulating that hypothermia as an aid to anæsthesia will reduce the risks of operation. But it is well that the physician should be aware that cerebral infarction can account for the neurological signs he observes in a patient with subarachnoid hæmorrhage, and that the surgeon also should appreciate the importance and frequency of this complication when he plans his surgical attack.

THE HISTORY OF FILARIA

THE work of great painters or poets remains with us today still fresh and enjoyed by many, but the work of great scientists is far less fortunate. It is buried under the additions of later generations of workers; and, although it serves as a foundation, it is all too often taken for granted or forgotten altogether. Yet the history of how these basic discoveries were made has still much interest and profit for the worker of today. Accordingly we should be grateful to Sir Philip Manson-Bahr for having told the story of one such discovery—that of *Filaria* (*Wuchereria*) *bancrofti*—in a readable and enthralling form.[1] His story is all the more authoritative because through his family and through his own work he has been connected with this subject from its early beginnings.

The tale is one of the best known in tropical medicine—how small worms (microfilariæ) were found in the urine and hydrocœle fluid of men with elephantiasis in the tropics; how Patrick Manson, a medical missionary, found that they appeared in blood during the night and disappeared during the day; how this led him to conclude that their behaviour must be correlated with some biting insect such as a mosquito which sucked blood at night and which could carry them from host to host; and how this led to the discovery of insect vectors of filariasis, malaria, and many other tropical infections. Besides the name of Manson, many other names should be recalled—M. Demarquay, O. Wucherer, J. Bancroft, T. R. Lewis, T. S. Cobbold, G. C. Low, and S. P. James.

Most of this work was done in the last twenty years of the 19th century, but the periodic behaviour of the microfilariæ has been further studied in recent years. It is now known that the disappearance of the microfilariæ from the peripheral circulation during the day is due to their congregation in the capillaries and small vessels of the lungs, perhaps because the physiological conditions there favour their survival. But if they stayed there all the time they would never meet a mosquito and so have an opportunity to be transmitted to another host. Apparently, the periodicity is a compromise which enables the microfilariæ to make the best of both worlds. They spend the day enjoying the favourable conditions of the lungs, and they come out into the peripheral blood at night hoping to meet a mosquito. If they are disappointed, they return to the lungs the next morning in order to rest and recuperate. Two phases of the cycle can be distinguished—a passive phase (at night) when the microfilariæ are evenly distributed through the blood and hence appear to be numerous

1. Symonds, C. P. *Quart. J. Med.* 1924, **18**, 93.
2. Richardson, J. C., Hyland, H. H. *Medicine, Baltimore*, 1941, **20**, 1.
3. Walton, J. N. Subarachnoid Hæmorrhage, Edinburgh, 1956.
4. Robertson, E. G. *Brain*, 1949, **72**, 150.
5. Clarke, E. S., Walton, J. N. *ibid.* 1953, **76**, 378.
6. Tomlinson, B. E. *J. clin. Path.* 1959, **12**, 391.
7. Wilson, G., Riggs, H. E., Rupp, C. *J. Neurosurg.* 1954, **11**, 128.

1. *J. trop. Med. Hyg.* March, April, May, June, July, 1959.

in the peripheral circulation, and an active phase in which the microfilariæ accumulate in the lungs. This accumulation cannot depend on opening and shutting of the capillaries of the host: it must be an active response by the microfilariæ themselves to some stimulus provided by the twenty-four-hour rhythm of the host; but the exact nature of this stimulus and indeed of many other factors concerned with microfilarial periodicity are still unknown.

One aspect which particularly stirs the imagination is the distribution of the two forms of *W. bancrofti*—the periodic and the non-periodic—among the islands and atolls scattered over the vast waters of the Pacific Ocean. When the Polynesians migrated in their canoes from one island to another, they presumably took their parasites and their mosquitoes with them. The more easterly migrants, presumably the earlier ones, carried the non-periodic filaria which is transmitted by *Aedes polynesiensis* and *Aed. pseudoscutellaris*; the less easterly (or later) migrants carried the periodic nocturnal filaria which is transmitted by *Culex fatigans*. The two areas are divided by a line which approximates to longitude 170°E. East of this line the people are Polynesian, malaria is absent, and the filariasis is non-periodic. West of it the people are Melanesian, malaria prevails, and filariasis is nocturnal. Thus the distribution of their parasites helps to give information about the prehistoric migration of these mysterious and romantic peoples.

ACTINOMYCIN D IN THE TREATMENT OF TUMOURS

Of the new anti-tumour agents (discussed in the symposium reported on p. 907), actinomycin is of special interest. First isolated in 1940 by Waksman and Woodruff[1] from a culture of soil actinomyces (*Streptomyces antibioticus*), it was found to have a strong action against gram-negative organisms, but was also selectively cytotoxic to mammalian tissues. Although too toxic as a clinical antibiotic, it was reinvestigated for its potential anti-tumour effect. Closely related compounds, designated actinomycin A, B, C, D, I, J, and X, differing only in the composition of aminoacids in the peptide side-chain of the molecule,[2] were soon isolated. Chemically, the various actinomycins are in fact mixtures of each other, and only actinomycin D is relatively pure.[3]

Actinomycin D was shown to act in mice against transplanted malignant melanoma, mammary adenocarcinoma, and leukæmia at doses of 75–100 μg. per kg. body-weight.[4] Parenteral treatment is essential,[5] and even administered parenterally the drug varies in its effect, although solutions of crystalline actinomycin D in 25% ethanol have proved stable for six weeks.[5]

Early clinical trials failed to show any benefit in children with acute leukæmia, but important temporary improvement was produced in rhabdomyosarcoma, Wilm's tumour, and Hodgkin's disease.[6] Moore et al.[7] studied the effect of the drug in adults with various forms of advanced malignant disease. With total doses of 50–75 μg. per kg. body-weight intravenously, divided into five or ten daily injections, objective temporary tumour regression was observed in only 12 of 67 patients (carcinoma of the breast 3, lymphosarcoma 3, carcinoma of stomach 1, melanoma 1, miscellaneous 4) and only 3 of these patients had remissions lasting more than a month. On the other hand, tumour cells disappeared from the blood, even when tumour masses remained unchanged. Slight marrow depression on the fourth to twenty-fourth day after the start of treatment was noted in a third of the patients, but usually recovered spontaneously within ten days. Other untoward effects included anorexia, nausea, vomiting, diarrhœa, buccal ulceration, acne, alopecia, an enhanced tumour growth-rate after ineffective therapy, and thrombophlebitis at the site of injection. (Excessive skin reactions over previously irradiated areas have also been reported.[8]) Maintenance therapy did not appear to be of benefit.

Tan et al.[8] at the Sloan-Kettering Institute have now reported their experience with actinomycin D in 111 children with metastatic cancer. Striking regression of massive pulmonary metastases occurred in several patients. The drug appeared to potentiate the predicted response to radiotherapy in 28 of 50 patients treated with approximately 50% of the estimated therapeutic dose of X rays, even in some relatively radioresistant tumours. Particularly interesting are the 49 children treated with actinomycin D alone, in 16 of whom objective tumour regression was attributable solely to the drug. In a 2-year-old boy with a Wilm's tumour a pulmonary metastasis regressed completely, and he has had no further recurrence for two years. In all, 6 of 16 children with metastatic Wilm's tumour who received actinomycin D alone showed objective improvement; indeed, Tan et al. suggest that this should be the initial form of therapy in such cases, with additive radiotherapy only if tumour regression is incomplete. Experience with other tumours was less favourable, although temporary benefit was observed in some cases of neuroblastoma, rhabdomyosarcoma, lymphadenoma and bone sarcoma. Similar results were reported by Pinkel [9] in a smaller series, in which objective temporary improvement in rhabdomyosarcoma and Wilm's tumour was also recorded. A $3^1/_2$-year-old girl with a recurrent rhabdomyosarcoma of the face had a particularly gratifying response, pronounced tumour shrinkage making a radical excision possible.

Although tumour inhibition with oral therapy could not be shown experimentally,[5] the Sloan-Kettering group, using oral doses of 3 to 10 mg. daily, estimated from the systemic effects that about 5% was absorbed. But the toxic effects on the gastrointestinal tract were more severe and commoner, preventing adequate therapy by this means. The recommended total intravenous dose is 75 μg. per kg. body-weight or 2–3 mg. per sq. m. body surface in three to six injections over a period of one to two weeks; but repeated courses may be needed in the absence of a suitable preparation for maintenance therapy.

The evidence suggests that actinomycin D may have a useful place in the treatment of disseminated Wilm's tumour and other metastatic sarcomas in children. Tumour shrinkage may make surgical excision possible; secondary deposits may regress following removal of the primary growth; and the effect of radiotherapy may be potentiated.

We regret to announce the death on Nov. 14 at Bungay, of Mr. Harold Wilson, consulting surgeon to St. Bartholomew's Hospital, London.

Sir Francis Prideaux, formerly director-general of the Ministry of Pensions, died on Nov. 15 at the age of 75.

1. Waksman, S. A., Woodruff, H. B. *Proc. Soc. exp. Biol., N.Y.* 1940, **45**, 609.
2. Pugh, L. H., Katz, E., Waksman, S. A. *J. Bact.* 1956, **72**, 660.
3. Waksman, S. A., Katz, E., Vining, L. *J. Path. Bact.* 1958, **44**, 602.
4. Farber, S. *Amer. J. Path.* 1955, **31**, 582.
5. DiPaolo, J. A., Moore, G. E., Niedbala, T. F. *Cancer Res.* 1957, **17**, 1127.
6. Farber, S., Toch, R., Sears, E. M., Pinkel, D. *Advanc. Cancer Res.* 1956, **4**, 49.
7. Moore, G. E., DiPaolo, J. A., Kondo, T. *Cancer*, 1958, **11**, 1204.
8. Tan, C. T. C., Dargeon, H. W., Burchenal, J. H. *Pediatrics*, 1959, **24**, 544.
9. Pinkel, D. *ibid.* 1959 **23**, 342.

Special Articles

THEORY AND PRACTICE OF PSYCHIATRIC DAY HOSPITALS *

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SOME twelve years ago the Social Psychotherapy Centre was opened in two war-damaged houses in Hampstead. It was in fact the first day hospital in this country, indeed one of the first in the world. In 1948 it became part of the National Health Service and in 1954 it was moved to roomier accommodation at St. John's Wood and renamed the Marlborough Day Hospital. Since then over forty day hospitals have been started in this country, and it seems worth while to review the ideas that lay behind the original Hampstead venture.

It was begun in the hope that the new arrangement would overcome some disadvantages of treatment in an ordinary hospital.

Inpatient Treatment

1. The illogical but real shock that some patients feel at being admitted to a mental hospital.
2. The danger of "institutionalisation" for a long-stay patient.
3. The breakdown of home ties and the difficulty of returning to normal life on discharge.
4. The expense of inpatient care.

Outpatient Treatment

1. The inadequacy of the treatment often offered.
2. The fact that patients who are not at work have the whole of the day to brood on their troubles.

But the methods developed at the Marlborough Day Hospital are more than an alternative form of hospital organisation. They are based on the principle that the genetic and physical and the dynamic and psychological factors of mental disorder are not opposites, nor even complementary, but parts of a whole. Treatment must therefore include the whole social environment of the patient and all his social relationships. He must be treated not only as a person but as part of a community.

Our Theory

We believe that the humanitarian period in the treatment of mental illness, in which everything possible is done to improve the patient's well-being, should be replaced by one of self-government. In this the patient is encouraged to do everything for himself and for his fellow patients. This necessitates the active cooperation of the patients and the clinical and administrative staff in creating a specially frank and friendly atmosphere in treatment.

The patient is in close and dynamic relationship with a number of therapists at the same time. He is treated by a therapeutic team, and he develops relationships with other people in the team—with the psychologist, the psychiatric social worker, the occupational therapist, and the social therapist, the receptionist, the nurses, other members of the staff, and other patients.

We call these relationships PATHER (PAtient-THErapist-Relationships). Clashes may occur but, given cooperation and a sound understanding of all the roles that may have to be played, differences are excellent material for analysis. Pathers are a useful method of overcoming the dissolution of the transference situation which has been called the graveyard of psycho-analytic treatment. When a patient is related to a number of people, the discontinuance of one relationship, even the most precious one, does not leave him in a state of shock and complete emptiness.

The therapist is in touch with a number of members of the patient's environment. This gives opportunity for different approaches, and helps both the patient and the people concerned with his welfare to accept the reality of the situation.

Our methods have enabled us to approach every type of patient, and no patient is refused admission. We consider that mental patients should be met in the same way as one meets and treats so-called normal people. Every human being, including every patient, belongs to a number of groups—i.e., family, school, club and so on—and his acceptance in these groups is essential for his wellbeing. The assumption that faulty relationships are the *result* of mental illness is probably onesided. We assume more and more that faulty or inadequate relationships are one of the *causes* of mental illness. In our experience treatment at a verbal and individual level seldom solves the difficult problem of faulty human relationships. Treatment of an experiential and situational nature, using the social group, is more effective. This point of view alters the role of the therapist. He is no longer the uninvolved Jupiter and he cannot escape the fact that, as he is living a life with his patients, he is an example to them.

In psychiatric treatment of this kind much depends on the staff's ability to create an atmosphere in which the patients feel that they are accepted as equals, that they can express themselves freely, and that they will be listened to. Our first step towards achieving this was to persuade the administrative and voluntary officers of the hospital to become members of the therapeutic team. They were encouraged to criticise and even interfere with the clinical side of the work. It is amazing how helpful such criticism of the so-called outsiders can be. Even when it is not, it gives opportunity for joint discussions and removes the barrier between clinical psychiatry and administration.

Our Practice

Our staff now consists of $2^1/_2$ senior and $2^1/_2$ junior psychiatrists, 13 paramedical helpers, 6 administrative officers, and 3 domestic workers. In 1957–58 we treated 1207 patients (679 new cases), and the attendance figure was 38,253. Our comparatively small unit could treat so many patients only by using group methods. Most patients wait six to eight months for admission, but urgent cases are taken in two to four weeks. In an emergency a patient is seen the same day.

To prevent our waiting-list becoming unwieldy, we select from time to time 20–30 patients for didactic group psychotherapy—i.e., the process of explanation and reeducation in a group session—or we invite, say, 6 patients to attend our therapeutic social club. They are asked to come an hour before the club meeting starts, so that we can have a talk with them and see that they are suitable, and so we can make personal contact. They learn to know each other a little, so that they join the new club as a group of acquaintances instead of each feeling alone among a great many strangers.

As we are short of staff, not every patient is seen by a

* Extracts from the Maudsley lecture given to the Royal Medico-Psychological Association, Feb. 9, 1959.

senior psychiatrist on his first visit. Those who already have a psychiatric report may be seen by a registrar, who will discuss the case with a senior psychiatrist or at the weekly clinical case conference.

At the diagnostic sessions we do not aim merely to fix a label. We also try to establish a rapport (PATHER), to find out the most important points of psychopathology, and to get as full a picture as possible of the total situation, including the patient's constitution, early childhood, siblings, and work record. Treatment is then arranged; and it may include occupational therapy, individual psychotherapy or group therapy of a didactic, analytic, or syntho-analytic type, group discussions, social club therapy, art, drama, or physical treatment (such as electroconvulsive therapy, lysergic acid, insulin, tranquillisers, abreaction).

Patients who attend the occupational therapy department have weekly group sessions with the medical director and with the psychologist. Every patient receives some form of individual psychotherapy, but because of shortage of staff we are not always able to provide as many treatments as we would wish. Individual psychotherapy, and especially a proper PATHER, is the basis of all treatment, including physical treatments and group psychotherapy.

The departments at the Marlborough Day Hospital are a well-integrated whole and often exchange functions. Thus psychiatric social workers not only look after the practical needs of the patients, such as work, accommodation, and contacts with welfare authorities, but also give valuable psychotherapeutic aid with patients and relatives. The psychologists are not only testers but also provide useful group and individual psychotherapy. The occupational therapists look after 50–80 of our most difficult chronic patients, often in ways which in other hospitals would be the work of the nurses. We are so short of nurses that they are only able to cope with the 10-bed unit where all patients who need physical therapy are treated. We have a small night hospital with accommodation for 10 patients, most of whom are in full-time employment. At the night hospital they are offered individual and group psychotherapy, and L.S.D.

Two clubs are run in the hospital, each with the help of a psychiatrist and a social therapist. Where it is more convenient, patients are sent instead to one of the seven clubs run by the Institute of Social Psychiatry in other parts of London. Our non-medical psychotherapist combines social-club therapy with acting-out methods, and our art therapist combines her work with a therapeutic club. Acting is also used as a form of abreactive treatment.

There is no division between our adult and children departments, for the parents are the most important part of the child's problems and treatment. The team is thus able to treat all members of the family without having to transfer them to another department. Apart from the normal family guidance service, we have for the past three years had a day school for psychotic and extremely difficult children.

We run training courses for psychiatrists, general practitioners, teachers, and others, and we give public lectures and hold discussion evenings for parents and teachers.

Discussion

Twelve years' experience has shown us many of the difficulties of running a day hospital and how they can be met.

In planning a day hospital it is advisable to place it in the centre of the area that it is to serve. Easy transport and communications are important.

Patients who give the impression that they are very ill should be separated from those who are not so ill, by using different houses. The division between psychotics and neurotics is not practical, for a patient with a major hysteria may be more disturbing than a patient with schizophrenia.

If the day hospital becomes too big it loses its personal character. This is one of the reasons why we favour an independent unit, and not a day department or day ward as part of a larger hospital. We try to create the atmosphere of a private house and we have found that this helps to relieve the apprehension of some patients.

If the waiting-list is allowed to grow too long, the number of patients being seen for diagnosis and the number of available sessions for treatment becomes disproportionate. Without watchfulness and flexibility it is easy to create a bottleneck.

Too abrupt discharges often lead to relapses. We find that a slow and gradual weaning is helpful. Instead of formally discharging our patients, we prefer to introduce them to our therapeutic clubs and allow them to grow away from us gradually at their own pace.

Our experience has proved to us that the great majority of mental patients can be treated on a part-time basis. We are convinced that a mental health service centred around a comprehensive day hospital, with a night hospital, therapeutic community hostel, therapeutic social clubs, self-governed workshops, and a small community service, could fulfil most future needs.

I am indebted to all the patients and the members of the staff for their cooperation, to Dr. T. M. Ling, Miss Kathleen Thompson, Mrs. Dora Bierer, and Commander V. E. T. King-Bull for constructive criticism, and to Miss Evelyn Baker for secretarial assistance.

Public Health

PROPHYLACTIC ISONIAZID

PROTECTION OF INFANTS IN A TUBERCULOSIS HOSPITAL

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TUBERCULOSIS is especially infectious in a family epidemic. Infants are the most susceptible of all humans to this infection, and in a malnourished primitive community they usually die. In the 19th century Grancher introduced in France the system of immediately separating the newborn child from its mother, which is still advocated by epidemiologists today. In countries where adequate institutional care, foster-mothers, and homes are available, this practice can be effective without causing too much physical danger to the child. In the so-called underdeveloped countries, it is as dangerous as tuberculosis itself.

In our hospital, which has over 1000 beds for Bantu patients with pulmonary tuberculosis, about 20 babies are born each year. Until 1955 these babies were separated immediately from their mothers, and sent to other institutions, foster-parents, or relatives.

Of the 17 babies born in 1954, 10 died in the first few months, and 5 could not be traced and were probably dead. As far as could be ascertained from the histories, gastro-enteritis, after a period of inadequate artificial feeding, was the chief cause of death. To nurse an artificially fed child in a primitive community is hazardous and difficult, and when the feeding is not carried out by the mother many of the children die.

Some of our mothers with their babies.

Faced with this appalling mortality-rate and encouraged by reports on isoniazid as a prophylactic against tuberculosis in guineapigs, we decided to keep all babies born in hospital with their mothers and to give them isoniazid as prophylactic.

Treatment

The child is kept in a crib by the mother's bedside, and from birth to six months is given 25 mg. of isoniazid in a syrup twice daily. After six months the dose is increased to 50 mg. twice daily. Up to date no adverse effects from the isoniazid have been noted.

Breast-feeding is the rule, and all the mothers who are well enough help with the care of their children. The children are in a 30-bed open ward, and all the women have active pulmonary tuberculosis. No special precautions are taken to prevent infection, and mothers are allowed to fondle their children as much as they wish. Mantoux tests are done monthly, and chest X-rays are taken two-monthly. The ward is a happy one: the contrast between it and other wards for Bantu women is startling.

Results

Between October, 1955, and January, 1959, there have been 101 confinements and 103 babies born (two sets of twins).

The Children

2 of the children were stillborn, and 3 died within the first three weeks. The remaining 98 have been in hospital for one to twenty-two months, the average length of stay being six months.

4 of these children became Mantoux-positive. They became positive within a few weeks of each other, at a time when the mothers were allowed to give the isoniazid to their children. Their mothers, for reasons unknown, had not been giving them the isoniazid. When this was discovered, it was decided that the nurses should give the children the isoniazid, and since then (two years ago) no other child has become Mantoux-positive while in hospital. The 4 children were given 20 mg. of isoniazid per kg. per day, and are all now well.

It has been impossible to follow up all the children after discharge, for most of them return to remote country areas; but the mothers have been advised to continue the isoniazid and to take their children to the nearest clinic for supervision. 22 of the children have been seen as outpatients —3 have become Mantoux-positive since discharge, after their mothers had stopped giving them isoniazid. 1 of the 3, a mongol, died of pneumonia after her primary lesion had cleared radiographically. The other 2 are well and chest X-rays are clear.

The Mothers

53 of the mothers had been treated for six to nine months before they were delivered. 22 of them had had less than three months' treatment; 36 of them had advanced disease at the time of the confinement, and 49 of them had positive sputum. 1 woman with very little functioning lung tissue died of cor pulmonale four weeks after delivery. 1, who had hæmoptysis before labour, died of hæmorrhage three weeks later.

Apart from these 2 deaths, there was no evidence of deterioration after pregnancy or during lactation. The disease appeared to behave as would have been expected in women who were not pregnant. Nearly all continued to improve. A few of the chronic cases remained unchanged.

All but 6 of these women breast-fed their children. 3 of those with chronic extensive disease had not enough milk, but begged to be allowed to feed with complements of dried milk. 4 children were weaned because the mothers did not wish to feed. 1 woman had had severe toxæmia of pregnancy, and 1 had puerperal psychosis.

Discussion

While it is always desirable, where possible, to keep a mother and child together, in a backward community this is life-saving. The mothers who have their children with them are the most contented among our patients, and the babies are beautiful thriving children.

From our three years' experience, it seems that isoniazid given prophylactically can completely protect a child from infection with tubercle bacilli. But a child so protected does not develop any immunity and, as soon as the drug is stopped, it will, if exposed, become infected.

We did not give B.C.G. to these children, as the conversion of the Mantoux test was our most important method of detecting infection. When the mothers leave hospital we cannot be sure that they will continue to give isoniazid as long as is necessary. Even if the mother's disease is cured, there is often living in the home an infected relative who refuses medical attention; so in future we intend to give isoniazid-resistant B.C.G. to all children before they leave hospital.

Summary

Isoniazid has been given prophylactically to 98 newborn infants so that they might remain with their mothers in a tuberculosis ward.

When isoniazid has been given regularly, it has completely prevented tuberculosis infection in the children.

The mothers have been allowed to breast-feed their children without adverse effects on mother or child.

". . . The human body was not evolved to suit the conditions of life today. It was evolved to meet the conditions of life, say, 25,000 years ago, when the great majority of human beings lived by hunting and food-gathering. As a consequence, in so far as our bodies are in fact suited to modern conditions it is so as a matter of accident. . . . One of the big problems that confronts biologists today is how can the human body be changed so that it may be more suitable for life in civilised society, and, perhaps more important, for life as it will be in the predictable future. . . . If we were spending money on biological problems at the same rate as we are now spending money on atomic energy and hydrogen bombs, we should soon have some of these important biological problems solved. It is, in fact, much more to the advantage of human beings at present to solve some of them than it is to have atomic energy available for industrial or for any other purpose. In biology, as in any other science, what comes out is proportional to the effort that is put in."—Prof. JAMES DANIELLI, *Listener*, Nov. 12, 1959, p. 825.

The Public Health in 1958

THE first few months of life continue to be the most hazardous, and progress in reducing perinatal mortality is comparatively slow: this may be one of the most important and difficult problems facing doctors today, in the estimate of the chief medical officer of the Ministry of Health, whose report [1] for 1958 appeared last week. Neonatal mortality changed little, though, because there were fewer stillbirths, the perinatal mortality-rate showed a slight reduction. Over 11,000 infants yearly fail to survive their birth by a month, and to this wastage must be added over 16,000 registered stillbirths—"a situation which certainly calls for intensive study". The detailed inquiry of the National Birthday Trust Fund into perinatal mortality is now in progress, and the coding and tabulating of the information gathered by questionnaire is being carried out by the Social Survey of the Central Office of Information.

The chief medical officer, Sir John Charles, also remarks that until means are found of preventing or improving the treatment of cancer and degenerative diseases of the circulatory system the present expectation of life is not likely to be appreciably extended.

The expectation of life in England and Wales has remained practically constant over the past five years though the proportion of persons over 65 has risen slightly from 117 per 1000 in 1957 to 118 per 1000 in 1958. Diseases of the circulatory system now account for over a third of the total deaths, and second in the hierarchy of destruction are the cancers, accounting for about a sixth. There is little sign of any halt in the rising trend in lung-cancer deaths over past years.

INFECTIOUS DISEASES

From 1943 until 1957 each year showed a fall in *diphtheria* notifications, but in 1958 the total jumped to 80 and there were 8 deaths. Altogether 25 local authorities notified cases during the year. But more than half (79) the local health authorities in England and Wales have now had five years or more without diphtheria (Canterbury has had none for twelve years). The number of immunisations (particularly reinforcing doses) has fallen during the past three years, especially among schoolchildren. "The programme for immunisation again poliomyelitis has greatly increased the work of local health authorities in the last two years, and this may have interfered with immunisation against diphtheria. . . . Events in 1958 should act as a warning to those who feel that diphtheria is a thing of the past and that an increase in its incidence is improbable. It is quite clear that there is still a danger that this disease could again become a serious problem and that efforts to maintain a high level of immunisation of children cannot be relaxed."

The incidence of *poliomyelitis* was 4·4 per 100,000 population, so 1958 was a relatively mild year. There was again a fall in the proportion of cases in the 5–15 age-group and a corresponding rise in the under-5 group. The higher incidence in males was more pronounced in 1958 than usual and was particularly evident in the 5–9 group. Only for paralytic cases in the 15–24 group was the rate higher in females.

About 14,900 cases of *food-poisoning* were reported during 1958, some 100 fewer than in 1957. As usual, processed and made-up meats were associated with most outbreaks. Reheated meat, meat pies, cold meats, brawn, pressed meat, and stew were most commonly incriminated. Six outbreaks were associated with freshly opened cans of meat: all the cans were imported.

VENEREAL DISEASE

There was a further fall in 1958 in the number of cases of early infectious syphilis attending clinics for the first time, but the decline was not consistent throughout the country. There was an appreciable increase in the Merseyside area and some increase also in Manchester and Tyneside. The Birmingham figures did not fall and those for London fell only very slightly. New patients in the later stages of the disease were also appreciably fewer than in 1957. The number of new cases of congenital syphilis in infants again fell, to 17 as against 27 in 1957. "It cannot be said too often that ante-natal blood tests provide the means of almost complete elimination of congenital syphilis and it is regrettable that such tests are not yet routine practice outside the ante-natal clinics of hospital and public authorities."

The continuing steep rise in new cases of gonorrhœa in both sexes, however, gave cause for anxiety. The rise is greatest in London and in certain other areas where immigrants from overseas are numerous. The report continues:

"Penicillin remains an effective remedy for this disease, but there has been a general tendency to increase the dosage which many venereologists have doubled or even trebled during the last few years. Even so, failures and relapses are quite common and there is reason to suppose that some patients who discontinue attendance after their symptoms have subsided are harbouring latent infection. Meanwhile, at the request of the Ministry, a Committee of the Medical Research Council is investigating the problem of the sensitivity of the gonococcus to penicillin.

"In London and in some provincial cities, prostitutes or 'near prostitutes' continue to be responsible for the spread of much infection, and the tracing, treatment and follow-up of these girls present a serious social as well as a medical problem."

TUBERCULOSIS

Deaths from all forms of tuberculosis in 1948 numbered 21,993 (19,088 pulmonary and 2905 other forms): ten years later the total was 4480 (3999 pulmonary, 481 other forms). The improvement in the younger age-groups was even more remarkable.

Since the peak of 1954 when 8728 cases of pulmonary tuberculosis were found by the Mass Radiography Service the number of cases has been falling. In 1957 3,154,600 (about 103,000 more than in 1956) were X-rayed, and the number of cases actually found was 6481, or 1·8 per 1000. "As the rate continued to decline," Sir John Charles comments, "mass radiography should become still more selective and still more closely integrated with the other chest and radiological services. It may be that a more appropriate designation for it would be selective group radiography."

MALIGNANT DISEASE

Discussing the early detection of cancer, the report declares: "The responsibility of early diagnosis is shared by the patient and his doctor. The patient has a duty to himself and to his doctor to avoid delay by reporting any suspicious signs or symptoms and he can help his doctor by a frank discussion of his fears. Ignorance, superstition, fear and procrastination interfere with the performance of this duty and the best means of overcoming these sets a public health problem of considerable complexity, only the fringe of which has so far been tackled."

From 1911 to 1920 deaths attributed to leukæmia in England and Wales averaged about 400 each year. During the past three years they have averaged about 2300. This increase is not peculiar to this country for there have been similar increases in all countries where adequate vital statistics have been compiled for sufficiently long. The latest figures showed that the highest recorded death-rates were in Denmark, U.S.A., and Sweden, and the lowest in Japan and Eire. A W.H.O. study found that mortality from leukæmia in all countries was high both in early childhood and old age but low during the intervening period of adolescent and early adult life.

MENTAL HEALTH

In the treatment of mental illness there was a shift of emphasis from hospital to community care: "in relation to almost every form of mental disorder there is increasing medical emphasis on forms of treatment and training and social services which can be given without bringing patients into hospital as

1. Report of the Ministry of Health for the Year 1958. Part II: On the State of the Public Health, being the annual report of the chief medical officer. Cmnd. 871. H.M. Stationery Office. Pp. 264. 12*s*.

inpatients or which make it possible to discharge them from hospital sooner than was usual in the past". The new Mental Health Bill reinforces this concept. The report points to a need for a comprehensive mental-health service integrated with other medical services and with the hospitals forming only part of it. Such a service should meet the mental-health needs of infancy and childhood, youth, middle age, and old age, and should deal with acute and sudden mental illness, with chronic and mild psychosis, with neurosis, and with psychosomatic disorders. It should also be concerned with all grades of mental defect and with psychopathy. "Reaching out into the preventive field and undertaking research, and at the same time improving the facilities for diagnosis, treatment, and prevention of illness, it finds methods of fostering good mental health. These things involve the hospital service, the local health authority service and the general practitioner, but far more than that they involve also the schools, industry, the universities, families, voluntary workers and the great general public; in fact, good mental health in a nation involves everybody in the nation."

Illness due to Aviation Oil

A widespread outbreak of illness in Morocco due to adulteration of cooking-oil with aviation oil has been reported.[1] Of nearly 10,000 people who became suddenly ill after eating the adulterated oil, more than 6000 have paresis of the legs. No deaths have been recorded.

The aviation oil, originally intended for rinsing out turbo-jet engines, was sold as machine oil at a U.S. Air Force surplus stores near Casablanca early this year. In September many patients arrived at Meknes Hospital complaining of stiffness in the legs; they walked with difficulty, and some used sticks or crutches. Since then cases have been reported from all over Morocco.

Twenty-seven merchants are reported to have been arrested and charged with diluting olive oil or peanut oil with the aviation oil and selling this mixture as cooking-oil. Under a law introduced on Nov. 4, the arrested men are liable to the death penalty for "crimes against the health of the nation".

Dr. HONOR SMITH and Dr. J. M. K. SPALDING, who went to Morocco at the request of the World Health Organisation, write:

"At the time of our visit the outbreak was sharply confined to Meknes and its neighbourhood. The paralysis is due to poisoning with tri-*ortho*-cresyl phosphate. The aviation oil is a synthetic lubricating oil made to withstand the very high temperatures that exist in turbo-jet engines. It contained nearly 3% of tri-cresyl phosphate; but most of this is the *meta*- and *para*- compounds, for oil producers are aware of the dangers of the *ortho*-compound and remove it as far as possible. Although the proportion of tri-*ortho*-cresyl phosphate was small, in Morocco all cooking is done in oil and some of the substances sold as olive oil contained as much as 98% aviation oil."

Inquiry on Anthrax

In 1957 the Minister of Labour and National Service set up a committee, under the chairmanship of Mr. R. F. Levy, Q.C., "to consider the existing legal provisions concerning the importation of goods infected or likely to be infected with anthrax and the precautions to be taken in connection with such imported goods for the protection of the health of persons and to make recommendations". Its report [2] appeared last week.

Present legislation relating to the handling of wool, goat hair, and camel hair is based on a review made during the 1914–18 war. Since then the pattern of trade has changed and there have been developments affecting methods of disinfection and medical treatment; and many people have urged changes in the law.

1. *Times*, Nov. 16, 1959.
2. Report of the Committee of Inquiry on Anthrax. Cmnd. 846. H.M. Stationery Office. Pp. 222. 12*s*.

The incidence and mortality of anthrax have fallen steeply: in the first decade of this century notified cases averaged just under 50 a year, and in 1948–57 the annual average was 23; deaths fell from 12 a year at the beginning of the century to less than 1 a year since 1945. The introduction of chemotherapy in the treatment of external anthrax has meant that nearly all patients recover provided the diagnosis is made early.

The decline in incidence has not been evenly spread over all the industries using materials that carry the risk. The committee separately examined the industries using wool, goat hair, and camel hair, industries using horsehair, bristles, hog and cow hair, &c., those using hides and skins, and those using other dangerous materials, such as bones and bone-meal. The committee also considered the risk to workers in docks, wharves, and warehouses from handling cargoes that might be infected. Internal anthrax has disappeared in the industries where most of the cases occurred in the past—i.e., those where wool and hair are handled. The incidence of external cases has been reduced to less than half, the reductions having taken place in the industries using horsehair, bristles, &c., and in those using wool and hair. The biggest problem remains in the handling of hides and skin, where there has been no marked reduction in the incidence of external anthrax and where internal cases, though rare, still occur from time to time. Only in industries handling bones and bone-meal has the disease increased. This has been a post-war development, and it is noteworthy that though they have never been known to cause internal anthrax, half the number of fatal external cases that have occurred recently were attributable to these materials.

RECOMMENDATIONS

Control of imports and compulsory disinfection.—On arrival in this country, common goat hair should continue to be disinfected at the Government Wool Disinfecting Station in Liverpool, but disinfection requirements should be modified for the finer varieties—namely, mohair and cashmere. The committee do not propose any extension of the compulsory disinfection requirements to materials that are not already covered.

Precautions in factories.—Where the basic precautions are not statutory, regulations should be made under the Factories Acts to require them up to the appropriate stage of processing in all anthrax-risk industries. This would make uniform and comprehensive provision for certain measures to be taken in all factories where there is an anthrax risk, and in some factories (for example those handling bones and bone-meal) would mean the introduction for the first time of special legislative requirements designed to safeguard workers against anthrax. It is also recommended that washing facilities should be provided in or near docks, wharves, and warehouses where goods that may convey anthrax are handled.

Early diagnosis and treatment.—Workers who may be exposed to anthrax should be issued with a card which they should show to a doctor when they report to him with any suspicious-looking lesion, so that he may have in his mind the possibility of anthrax. The Factory Inspectorate and the Health Service should together make the most effective arrangements for early reference of suspected cases to a doctor, either in hospital or general practice, who is aware of the anthrax risk. Such arrangements might take the form of bracketing particular factories, warehouses, and docks with designated hospitals, forewarned that workers in these factories were exposed to the anthrax risk, or of alerting general practitioners that there were in the area certain work places where workers might contract anthrax.

Other recommendations.—Anthrax should be made a notifiable disease under the Public Health Act, as well as under the Factories Acts, and notifications of cases should be watched to ascertain, in particular, the incidence among users of bone-meal fertiliser so that consideration can be given to the question of further preventive measures. Possible future developments, such as immunisation against anthrax and disinfection of anthrax-bearing materials by ionising radiations, should be kept under review.

Caravans as Homes

My mother said that I never should
Play with the gypsies in the wood.
If I did she would say
Come along gypsies and take him away.

Childhood nursery-rhymes like that still seem to colour our national outlook on the people who live in caravans all the year round. We may have a whimsy regard for the myth of capturing the scent of Romany life on a brief caravan holiday, however much we fret at the overtaking difficulties on the open road. We may thankfully accept the static caravan as a summer chalet, tucked silently away in the trees, or as number ninety-six in a crowded jolly seaside camp. But we look rather sideways at permanent caravan life: we are reluctant to concede them even the title of homes. Yet how unfair may be our superficial judgments.

Sir Arton Wilson blows the wind from the heath through a lot of our deepest prejudices in a most refreshing whitepaper. He calls it *Caravans as Homes*,[1] which immediately recognises the dignity of the people who live there. He specifically excludes gypsies, but not the hostility that lingers towards them. He excludes most of the other itinerant caravan dwellers, but not the suspicion of nomads that has haunted static communities since time began. The nursery-rhyme is not far below the surface of our adult life.

All Sir Arton Wilson was asked by the Minister to do was to get the facts about residential caravans and see what the problems are today. The social-survey division of the Central Office of Information were called in to help. The results seem to show that something needs doing, but just what and how are battlegrounds for conflicting interests. As the report says, the people who live in the caravans seldom participate in public controversy: they are merely the people that the controversy is about. All they ask is that, as long as they have to live that way, the public authorities should help and not harry them. It sounds a fair enough proposition to put before the Government.

About 150,000 people now live in some 60,000 caravans all the year round, but 80% of them say that they would like to give it up as soon as they can get an ordinary house of their own. That is perhaps the most telling point in the whole report. It puts the major responsibility fairly and squarely on the local authorities to build more houses. The local authorities have been the loudest grumblers against permanent caravan sites: they have used their limited powers to carry on a guerilla rearguard action against the infiltration of caravans. They now have a clear choice: either to find permanent houses to replace the caravans or to run the sites themselves. If the people want an ordinary house or flat or bungalow, and are willing to pay for it, someone ought to meet the demand, either by private enterprise or by public effort. If private site operators are not doing their jobs properly, then public authorities should provide some better permanent caravan sites. Local authorities have ample powers to do both. It is nothing but wishful thinking to expect the caravanners to melt away like the gypsies. They are here to stay—unless they can be fixed up in some better style.

Actually it is a half-truth to say that they are here to stay. The caravans may be, but the folk living in them will not. It is worth looking to see just who they are. About a quarter of the residential caravans—some 15,000 little homes—are taken up by newly married couples who moved straight into them. Nearly the same again (about 13,000) contain more young married couples whose first homes had let them down for one reason or another: landladies, mothers-in-law, no privacy, or no room for the baby. Yet another 13,000 vans are used by people who have come into the area to follow some local expansion of industry. New factories need workers: new workers need homes: new homes mean caravans unless someone builds houses.

So two-thirds of the caravan dwellers are young healthy vigorous stock, decent honest people, earning good money—which in truth they need for the surprisingly costly privilege of caravan living. They have a stake in their local community and its economic prosperity: they want to bring up their families in something better. That is why they are not here to stay. There is a steady turnover as the lucky and the enterprising find an answer, but another batch of newly-weds are moving in as fast as the others move out. Unless we accept the principle of a term in the wilderness for young families, the only remedy is to build 40,000 more houses where they are needed.

The other third of the caravan homes do not seem to call for such urgent attention. About 6000 are used quite contentedly by more elderly people who choose to live in some pleasant spot. About the same number again are cheerfully accepted by families whose work perforce keeps them moving from time to time. Something less than 10% belong to the outdoor-life enthusiasts. The question remains whether the overall one-third group, of some 20,000 caravans, should be accepted by the whole community as an integral part of our way of life, today and tomorrow.

There are a lot of ways of looking at such a question—town and country planning, the preservation of green belts and amenities, the provision of local services, schools, buses, and shops, all the lucrative commercial interests of the caravan site operators, the caravan makers, the land owners, the rating aspects, and so on. Those issues will all have to be fought out. But Sir Arton Wilson also touches upon some more purely medical points of life in caravans. On the whole the people who live in them seem no better or worse in health than the rest of the population. Perhaps this is some tribute to the makers of the vans and the supervision of the site operators. Certainly it is more difficult to look after ill people in a caravan, and so they are much more likely to need moving to hospital, and indeed moving for many of the other social crises of life. No-one could feel too happy about having a baby in a van, or rearing a large family, or taking in a frail and elderly relative. The fire risks are greater, and the accident risks may be too; the physical strains are harder; the cramped space may induce a better self-discipline of tidiness, but it probably takes its toll in nervous tension and family relationships. Epidemiologically these sites need watching all the time. Sanitation is often primitive, and communal standards are apt to slip to those of the lowest common denominator. There are good sites and bad sites, and the law does not do much to enforce or encourage their improvement.

Those of us who sit by the fire in our houses are left with the uncomfortable feeling that we are not doing all we should for most of the caravanners. The nursery-rhyme is not really a valid excuse for chasing them away. They are not even gypsies.

1. Cmnd 872. H.M. Stationery Office. 5*s*.

Control of Radioactive Wastes

The Government has decided to extend and unify the controls over the discharge of radioactive wastes. Hitherto, and apart from the arrangements applying to the Atomic Energy Authority, risks to public health have been avoided principally through cooperative arrangements between central and local government. But on the advice of an expert panel, under the chairmanship of Dr. A. Key, senior chemical inspector, Ministry of Housing and Local Government, the system is to be revised. The Radioactive Substances Bill, published last week, provides that:

(1) Temporary controls (which bring under the control of the Minister of Housing and Local Government and the Minister of Agriculture, Fisheries and Food—in Scotland, the Secretary of State—any discharge of radioactive wastes by the Atomic Energy Authority and other licensed nuclear installations) will be made permanent.

(2) Other users of radioactive materials will be obliged to register their premises with the appropriate Minister (in England and Wales the Minister of Housing and Local Government, and in Scotland the Secretary of State).

(3) No disposal of radioactive wastes will be permitted except on an authorisation from the appropriate Minister or Ministers.

(4) The Minister of Housing and Local Government and the Secretary of State for Scotland will, in addition, have power to arrange a national disposal service to handle wastes which cannot safely be dealt with in the areas in which they originate.

The panel's report appears in a whitepaper [1] published with the Bill. They recommend central control because, apart from special provisions which apply to the Atomic Energy Authority, existing controls governing disposal of radioactive wastes are the same as those governing ordinary wastes. None was specifically designed to cope with radioactive wastes, and some can be applied only when harm has started to be done. While some release of radiation is inevitable in the development of nuclear power and research and the industrial use of radioactive materials, wastes can generally be disposed of by methods commonly in use by sewerage and sanitary authorities for the disposal of ordinary wastes, provided always that adequate precautions are taken. Local disposal of wastes can safely continue in many instances, thus avoiding the risk of increased exposure through multiple handling.

The whitepaper says that hitherto concentrations of radioactivity in wastes such as might involve risk to public health have been effectively avoided by administrative action. The new Bill gives effect to the panel's recommendations, and replaces certain powers now held by local bodies. It provides in appropriate cases for consultation with and supply of information to local authorities on the whereabouts of radioactive materials and on methods of disposal. The reason for having a register of users of radioactive materials (other than A.E.A. and licensed nuclear installations) is to impose a control at source. Registration in itself is not an authorisation to dispose; each undertaking, once registered, must submit its proposals for disposing of radioactive waste and get them authorised.

1. The Control of Radioactive Wastes. Cmnd. 884. H.M. Stationery Office. Pp. 46. 2s. 6d.

Mental-health Services in Cumberland

In his 1958 report Dr. W. H. P. Minto, medical officer of health for Cumberland, suggests that the chief difficulty which even progressive rural local authorities will face in providing community care for the mentally ill is shortage of adequately trained and experienced workers. In Cumberland, for instance, the post of psychiatric social worker has been vacant for four years and still remains unfilled. These difficulties of recruitment he attributes not only to unattractive salaries and promotion prospects, but most of all to the lack of a nationally agreed scheme of training and the resulting inadequacy of university tutorial courses. To try to meet this need Cumberland has started a scheme for " in-service " training for general mental-health workers and a scholarship scheme to encourage social workers to train for psychiatric social work. But even with schemes of this kind Dr. Minto foresees that the rate at which trained staff becomes available will not keep pace with the demands for their services. He believes that shortage of staff will be a greater hindrance to the working of the new Mental Health Act than lack of money for the development of homes and training-centres.

Symposium

ANTIBIOTICS

THE 7th annual symposium on antibiotics, organised by the journals *Antibiotics and Chemotherapy* and *Antibiotic Medicine and Clinical Therapy*, took place in Washington, D.C., on Nov. 3–6. Dr. HENRY WELCH, of the U.S. Food and Drug Administration, was in the chair. Over 800 doctors attended and 246 papers were presented, including contributions from 22 countries other than the U.S.A.

Antibiotic Resistance

In a burns unit at the Medical College of Virginia Hospital (150 severely burned patients annually) B. W. HAYNES and his colleagues, in wound culture experiments, noted that penicillin, streptomycin, and the tetracyclines approached 100% ineffectiveness with use. Nasal cultures from unit personnel showed coagulase-positive staphylococci in approximately 25% throughout the year. Similar rates were found amongst the staff of a surgical ward in Washington (W. W. WRIGHT), and increasing resistant rates, both to penicillin and tetracycline, were observed in the nasal passages of patients in a rheumatic-fever convalescent home in Chicago (M. H. LEPPER). Staphylococcal resistance to antibiotics has led to increased investigations of non-antibiotic chemotherapeutic substances, such as the nitrofurans and bisquaternary diamines.

Penicillins

First reports are now available about potassium α-phenoxyethyl penicillin (BL P152), a combination of two diastereoisomeric forms (' Syncillin '). Following the work of J. C. Sheehan in the U.S.A., who first converted penicillin G to 6-aminopenicillanic acid (and synthesised penicillin V), and the English workers Doyle and Rolinson, who found an economic source of this compound in fermentation broths, the synthesis of innumerable new penicillin compounds is now possible. Over 500 have already been prepared by Bristol Laboratories, and, as reported by Dr. WELCH in his opening address, by the manipulation of sidechains broad-spectrum, antifungal, antiviral, and anti-tumour penicillins may be future chemical possibilities.

In animal protection tests penicillin P152 was more active than penicillin G or V; it was not irritant when given intradermally, intramuscularly, or even intrathoracically; and peak serum concentrations after oral administration were substantially higher than with comparable doses of penicillin V. Similar dose-for-dose blood levels have been obtained with P152 by mouth as with benzylpenicillin G intramuscularly. There was some suggestion that the new penicillin was more active than the others against certain pathogenic bacteria. It was more resistant in vitro to *Bacillus cereus* penicillinase than penicillins G or V. In 762 persons so far treated with P152, mainly by G. A. CRONK and associates (Syracuse) and by E. M. E. MORIGI (Philadelphia), only 1 doubtful case of allergy was noted. But previous penicillins have often been believed to cause fewer allergic reactions, only to disappoint with wider use.

Streptomycin

W. H. HARRISON (Chicago) presented some striking audiograms of irreversible and sometimes severe nerve deafness after even small doses of dihydrostreptomycin (and in some cases after kanamycin and neomycin). Dihydrostreptomycin had been mixed with penicillin in a number of preparations, and Dr. WELCH announced that the use of dihydrostreptomycin in combination with penicillin has now been banned by the U.S. Food and Drug Administration. The only antibiotic with which it could be mixed was streptomycin itself and its toxicity on the eighth nerve must be stated on the label. There was scope for research in Great Britain into the extent of aural damage dihydrostreptomycin may have caused. Deafness may not appear for some months, so the association may not be appreciated.

Chloramphenicol

An analogue of chloramphenicol, dextrosulphenidol, was tested in vitro against the gonococcus by J. D. THAYER and his associates (Chapel Hill, North Carolina) and compared with kanamycin, leucomycin, and chloramphenicol. It proved the most active. W. GARSON showed it to be 8–32 times more effective in experimental syphilis than chloramphenicol. It was suggested that its toxic effects (hæmopoietic) might be offset in man by the much smaller dose necessary.

Tetracyclines

Tetracycline (1 g. daily) was given for three months in chronic bronchitis by P. S. NORMAN and his colleagues (Baltimore). Benefit followed 21 out of 39 treatments, compared with only 11 out of 39 with a placebo. J. McC. MURDOCH (Edinburgh) described a double-blind trial in which oxytetracycline (1 g. daily) or dummy tablets were given for six

months for chronic bronchitis. Of the 40 patients receiving dummies 27 were off work for 358 days during the winter, while 23 of the 26 patients completing the full course of active treatment remained at work and the total of 35 patients in the treated group lost 210 days.

A new derivative, dimethylchlortetracycline (D.M.C.T.) ('Declomycin', 'Ledermycin'), has been found to produce higher and more persistent blood levels than either chlortetracycline or oxytetracycline and it is excreted at only 43% the speed of tetracycline. Susceptibility tests on over 850 strains of 15 bacterial pathogens were reported by M. FINLAND (Boston). The drug had a similar range to other tetracyclines but proved effective against some strains resistant to tetracyclines. L. P. GARROD (London) reported that D.M.C.T. was twice as active as tetracycline against some organisms. Given to 48 medical students it was well tolerated and the number of bowel actions (1·4 per day) were no more than with other tetracycline preparations. In gonorrhœa M. MARMELL and A. PRIGOT (New York) reported that the necessary dose (600 mg. for one or two days) was almost as small as that of tetracycline by injection. All but 2 of 62 patients were cured.

Another tetracycline compound described was pyrrolidinomethyl tetracycline. M. A. KAPLAN and his associates found that single daily intragluteal injections of 350 mg. gave serum concentrations which should be adequate for the treatment of most susceptible infections. Single injections of 250 mg. were reported by R. R. WILLCOX (London) to be followed by 30% of relapses in gonorrhœa, though they were less painful than the same dose of tetracycline phosphate with lidocaine in which 42% of failures were noted (16·7% if 500 mg. was used).

Other Antibiotics

Triacetyloleandomycin gave good results in hospital staphylococcal infections (M. LEFEBVRE, Montreal), in preventing the emergence of resistant organisms, in upper respiratory infections in children, and in dermatological conditions. Y. D. ESKELSON (Salt Lake City) claimed good results in 79 of 85 cases of acne. T. W. MOU (New York) used it for rheumatic-fever prophylaxis and concluded that while penicillin was the antibiotic of choice, triacetyloleandomycin was worth further trial in patients allergic to penicillin.

L. D. ASAY (Los Angeles) reported the use of *ristocetin* in 90 infants and small children, 57 of whom had serious staphylococcal infections. 82 showed a favourable response but eosinophilia, neutropenia, thrombophlebitis, and cellulitis were among the side-effects noted. Local complications could be reduced by combining the antibiotic with cortisone.

Kanamycin was tested in experimental syphilis by T. C. WASHBURN and associates (North Carolina) but the large dose required for cure suggested that it was unlikely to be useful in the human disease. In gonorrhœa M. MARMELL stated that all of 25 patients were cured by 3 g. given intramuscularly over three days and 54 of 56 given 1·5 g. over the same time. Other workers showed that 50% of the blood level of kanamycin could be found in the bile and 26% in the pancreatic juice. A specific chronic toxicity on the cochlear nerve was observed in animals.

Antibiotic Combinations

A. M. TORRA (Uruguay) reported a delay in the emergence of staphylococcal resistance when a combination of tetracycline and oleandomycin was used. This combination was given by M. S. GREIF (Austria) for cholecystitis, and negative bile cultures were obtained in 78 out of 80 patients after four or five days. Other workers reported its successful use in "pneumonopathies", upper respiratory infections in children, serious surgical staphylococcal infections, intestinal amœbiasis, gynæcological infections, and syphilis.

Little data were presented concerning antibiotic/steroid combinations, but J. KIRBY and associates (Washington) had conducted a controlled blind study of 42 patients with pneumonia. 33% were afrebrile twenty-four hours after tetracycline alone, compared with 72% when steroids were given as well.

Antifungal Antibiotics

Amphotericin B has proved lifesaving in systemic fungal disease. G. L. BAUM (Cincinnati) used it in 6 cases of histoplasmosis, 5 of North American blastomycosis, and 2 of cryptococcosis. 1 of the histoplasmosis patients died of lung cancer, but the others were well three to eighteen months after treatment. The antibiotic may produce undesirable and sometimes grave side-effects.

Griseofulvin is active orally against a variety of fungi associated with dermatophytosis in man and animals. H. BEHRMAN et al. (New York) treated 97 children with tinea capitis. Negative cultures were obtained four to thirteen weeks after treatment. N. J. GOLDFARB (New York) found griseofulvin of definite use in the treatment of tinea cruris, which responded rapidly to 1 g. a day. Gastric distress was caused in some patients, and instances of psychic stimulation had been reported.

Anti-tumour Antibiotics

Experimental evidence indicated that certain antibiotics had strong anti-tumour effects on specific animal neoplasms. Studies of these drugs (called "antimitotics" at a symposium held in Geneva earlier in this year) may yield information leading to a trial against human cancer.

KANEMATSU SUGIURA (New York) tested 29 antibiotics against 19 solid tumours of the mouse, 7 solid tumours of the rat, 3 hamster tumours, 3 ascites tumours of the mouse, 1 mouse leukæmia, 1 mouse virus leukæmia, and 1 chicken tumour. The first intraperitoneal injection of the antibiotics at maximum tolerated doses was given one to seven days after tumour transplantation and injections were continued for seven days. Mitomycin C was possibly the most effective, followed by fumagillin, 6-diazo-5-oxy-L-norleucine, the actinomycins, actinobolin, sarcomycin, and streptovitacin A.

Mitomycin C, which was used on 663 malignant cases in Japan last year, was described by YAEMON SHIRAHA (Osaka). Of 194 cases treated the disease was inoperable in 151, and 43 others were given mitomycin C postoperatively to prevent relapse. 3 patients of the 151 with advanced malignancy (maxilla, bladder, stomach) were well ten to twenty months after treatment began.

Two new anti-tumour agents, *streptonigrin* and the *diazomycins*, had been tested by KOPPAKA RAO and his associates (New Jersey). Streptonigrin, prepared from the culture filtrates of *Streptomyces flocculus*, was active against adenocarcinoma 755 but only moderately active against sarcoma 180 and leukæmia 1210. The diazomycins, which showed a high activity against sarcoma 180 and adenocarcinoma 755 in mice, together with another aliphatic ketone (6-diazo-5-oxynorleucine), formed the active principle of the broth yield of *Streptomyces ambofaciens*.

New Antibiotics

The most promising new antibiotic was perhaps *colistin*, prepared as the sulphate 'Colymycin S' or the methanesulphonate 'Colymycin M'. These are two new forms of the antibiotic obtained by Koyama and his associates in Japan from *Bacillus colistinus*. Dr. B. S. SCHWARTZ et al. (New Jersey) reported that they are basic polypeptides resembling polymyxin, though the chemical and pharmacological actions are different. The methanesulphonate is appreciably less toxic in animals than colistin sulphate which may cause stomach ulceration in rats. Neither form is absorbed appreciably from the gastrointestinal tract. A. BLAUSTEIN (New York) reported that the drug was very active in man against *Pseudomonas pyocyanea*, *Escherichia coli*, *Bacterium aerogenes*, and other gram-negative organisms. It was successfully used in wound infections in burns infected with *Pseudomonas aeruginosa*, and in children suffering from gastroenteritis due to *Esch. coli*; and fair results were obtained in salmonella enteritis.

Aspartocin, prepared from *Streptomyces griseus* var. *spiralia*,

was said to be effective against a number of penicillin- and tetracycline-resistant staphylococci.

'*Humatin*' (*paromomycin*), which is not yet in production, is a new anti-staphylococcal antibiotic which is claimed to be of use also in intestinal amœbiasis.

Medicine and the Law

Medical Evidence in Nullity Suit

A HUSBAND petitioned for a decree of nullity of marriage on the ground that his marriage had never been consummated owing to the wife's wilful refusal and, alternatively, her incapacity. In accordance with the usual practice in this type of nullity suit, the medical evidence was heard in camera and judgment was delivered in open Court.

Mr. Justice SACHS said that the marriage took place in 1934. Evidence relating to the wife's gynæcological condition had been given by three women doctors. Dr. W., the medical inspector appointed by the Court, who saw the wife in January, 1959, and again on Nov. 6, 1959, and Dr. M., who saw her about the beginning of November, 1959, both thought that at the time their respective examinations took place, sexual intercourse was not practicable. There was, however, an apparent conflict between these two doctors on the question whether sexual intercourse had been practicable in earlier years.

Dr. M.'s evidence indicated a difference between the condition she found and that found by Dr. W. in January, 1959. As a result, Dr. W. made her second examination after the hearing of the suit had started. She then gave further evidence to the effect that there was a marked difference between the condition of the hymen on the second examination and its condition in January, 1959. At that stage, it emerged that the wife had also been examined in January, 1959, by Dr. L., who had been assured by the wife's solicitors at whose request the examination she made had been carried out, that she would not be required to give evidence. The report Dr. L. had made of her findings was of very great brevity. She went into the witness-box, having no notes of what she had observed, or the inferences to be drawn from her observations. She had contented herself with making the gynæcological examination in such a way as to rely on feeling alone, without a visual examination. She relied on her memory rather than making a careful note such as a doctor should, and usually did, make when carrying out an examination the object of which was, or might be, to provide evidence in legal proceedings. In the result, her evidence was far less impressive than that of Dr. W., with which it was in conflict, and the latter's evidence was therefore to be preferred.

His Lordship held that at all material times the wife was unable to engage in sexual intercourse, but that a minor operation would probably have rendered coitus practicable. He excluded from consideration the possibility of hormone treatment, which had not been proved to have been available throughout the material period, and which he did not think would have been prescribed by the average medical practitioner. He accepted the legal argument that where a wife who was unable to engage in sexual intercourse, and whose incapacity could be removed by a minor operation, refused, without adequate reason, to undergo that operation, the case was one of wilful refusal rather than incapacity. He granted the husband a decree *nisi* on the ground of wilful refusal.

DICKER *v.* DICKER (otherwise PARRIS)—*Probate, Divorce and Admiralty Division:* Sachs J., Nov. 9, 1959. Counsel and solicitors: R. J. A. Temple, Q.C., and D. Peck (John Lester & Co. Hastings); K. B. Campbell and B. Anns (Perring & Co. Hastings).

D. R. ELLISON
Barrister-at-Law.

In England Now

A Running Commentary by Peripatetic Correspondents

IT was one of those brilliant autumn mornings with more than a hint of winter. A cheerful sun gave colour to the park, but the coldness of the air caused groups of birds to stand motionless and unblinking—gulls at the water's edge, pigeons and ducks on the grass or the path. The spontaneous animation of summer was gone and there was a delicate haze above the water.

In front of me on the footpath I saw a young woman, sauntering along behind a pram. She wore black stockings, ballet shoes, a coat with an astrakhan collar, and a white fur hat. Charles Lamb would have enjoyed the describing of that hat, but I will only say that it conveyed a delicious impression of sumptuous warmth, at once caressing and protecting the smooth black hair and tender ears of the exotic young mother. And as she strolled, idly rocking the slowly moving pram with one hand, she held in the other a paper-backed book, glancing now at the page, now at the mist-veiled autumn trees, now at her son, who, balancing in the enormous pram, was gazing at her with the gravest possible fixity.

My heart (rendered unstable by the weather) gave a kick. This girl could only be a living sequel to Anna Karenina. An oblique glimpse of her features confirmed that she might easily be a White Russian aristocrat, of the old, slender days before the broad-beamed peasant ruled the salons. But then I became doubtful. Was it not more likely (thought I) that here was some child of Ilford or Tooting, living now in Chalk Farm and yearning above all to be *kulturny* like the Hampstead lot? Her husband, whatever he might be, certainly not an ex-diplomat discreetly retired to live in Regent's Park after a rash hasty marriage to the *prima assoluta* of the Bolshoi? I remembered the 29,000 English buyers of the B.B.C. pamphlet *Russian for Beginners* and the whole pathetic imposture now seemed clear.

I quickened my pace and drew alongside. I saw the title of the book, *Essential English for Foreign Students*. Scepticism tottered. Calling B.B.C. lesson 2 to my aid, I gave a formal bow and said " Zdravstvuytye! " She gave me a breathtaking smile and murmured: " Zdrastye!" There was nothing more to be said, so I lit an imaginary black cigarette and passed on, inhaling deeply and looking as much like Vronsky as I could. In a way, I wish she had used the familiar form, " Zdravstvuy!" But I don't know. Something would have been spoiled if she had.

* * *

I have just been moved out of the main ward into a cubicle. This is, in some ways, more public, but it is auditorally speaking more private, and the other was—mildly—down-getting. You see, to be in the swim one had to enjoy one's bowels, as it were, and share them generously with one's neighbours. But something in my upbringing makes me keep mine to myself and so I was rather out of things. Then there was the curtain round my bed. Everybody came to see me. People I have quarrelled with at lunch for years started with surprise as they passed my bed saying: " Well well! that's who you are. You know I have been hearing about you for years. I read your paper on whatnot. And to think I have sat next to you so many times. Isn't it extraordinary?" I just had to relax and grin. We obviously all know one another so well that I couldn't ask the nurses who they were. The curtain shielded me from all this, and I listened to the light programme behind it, with a suffering, soulful, third-programme expression in case Sister or the H.P. turned up. Then an old friend arrived, and carefully drew it back so that we gossiped in full view. " I think this is wise ", he said; " you only draw that if you are Up the Wall; and as the Director of the Psychiatric Department—I think this is probably easier in the long run. Other patients don't understand ". But after he had gone, Sister drew it again.

Still I now have a cubicle. This means I am very ill. Probably on the Danger List to the other patients, but I feel better.

I sally forth at dawn and disperse thirty-five teas. I was the assistant, but now I have got it organised, except that I forgot the other cubicle this morning because she is on special milk. Before Sister comes on I revert to my complete rest in bed having avoided atrophy of the walking and pouring-out muscles. In my cubicle I miss the husky whispers at dawn: "Who was took really bad last night?" I miss the speculations about the home life of Dracula who grins and hums as he takes the blood. I have fewer ward-callers, less "Do you get those wrenching heaving feelings?" But I don't have to enjoy it all publicly, and, apart from the fact that that high duster must be full of awful staphylococci, and my diet is composed of cardboard (choice between dry and soggy), I can assure readers that all is well in ward *Chez-nous*.

* * *

I'm really enjoying committees now, instead of finding them a burden and a bore. They are such an excellent way of keeping up to date with the literature. I look forward to a restful hour or two, and come away with the feeling that I have accomplished something. It is quite simple. *The Lancet* and other journals are strewn out and mixed with the agenda, reports of subcommittees, and so on. No-one notices. Much of the agenda of our large hospital committees is irrelevant, and it is possible to keep sufficiently in touch to intervene when the interests of one's electors are at stake. If everyone did the same, meetings might be much shorter.

* * *

The plane landed at Orly and we passengers-in-transit (an ever-enlarging subspecies of the Hominidæ) were shepherded to a suite of rooms, there to be incarcerated until the voyage could be resumed. Spirits, perfumes, and cigars were readily available at duty-free prices, but what about postage stamps for the letters we had written over the Atlantic on the paper so thoughtfully provided?

At the newstand I was told "By law we can sell stamps only to those buying postcards from us, but there's a post office on the lower floor." So down I went. *Postes* greeted me a few yards from the foot of the stairs. But an *agent* held up his hand; I had not legally entered French territory and, therefore, *Postes* was out of bounds for me.

Troubled times demand vigorous action: an air-line's employee (I never learned his status) will probably remember the man who threatened to start a bonfire in the room, in protest, unless the promise made on the plane to despatch our letters was fulfilled. It was.

Four hours later, I arrived at Athens airport, again with a letter written on paper thoughtfully furnished by the stewardess. This time I was prepared to denounce the entire Cyprus agreement, should it be necessary, to get a stamp. But it wasn't. Rumour led me to the souvenir stand. "Yes, we sell stamps." But not directly, it appeared. The girl took my coin, filled out a sales-slip in duplicate, tore off the original, invited me to accompany her. We walked down a short corridor to another room. There she handed the slip and the money to the cashier who took my letter and then gave the change to the girl who turned it over to me. The Cyprus agreement still stands as far as I am concerned; Grivas can fend for himself.

* * *

SUJET PERDU

They didn't serve
Hors d'œuvre
The *pommes* were *purée*
Much to my fury
(I could have borne that meat
With *frites*)
And I'd rather forego
Estonian *Bordeaux*
Hélas!
The worst was yet to come to pass
When I forgot the speech I had prepared—
C'est de la —— *!*

Letters to the Editor

EXTRADURAL HÆMORRHAGE

SIR,—Although it is obviously wrong I have always assumed that we should be able to save the life of every patient with an extradural hæmorrhage. As each one has come to necropsy I have gone through the record to see how they might have been saved. I certainly agree with Mr. Eastcott (Nov. 7) that one important cause of their death is removal to a recognised neurosurgical centre. Once the diagnosis is made there may be no time for this, and some of my necropsies have been on those who have died on the way or very soon after arrival at the centre. Each town lacking a neurosurgeon should have a general surgeon able to give the necessary treatment.

The diagnosis of extradural hæmorrhage has rarely seemed to me to be difficult: the history and the "compression pulse" are usually clear enough. Much more difficult is where to operate. The extradural hæmorrhage may be anywhere from the centre of the frontal to the centre of the occipital bone. I have never seen at necropsy a case where the linear fracture was not an excellent guide to where the operation should take place. I consider exploratory burr-holes far too chancy. We should not hear that there was no time to take good radiographs: there is too little time to do without them. To me it is surprising to read that a bruise is thought a better localising sign than the fracture. Bruises may be absent, exceedingly large, or multiple. If one bruise is placed over the fracture the operation site will be clear. I hope the bruise will be used to help the radiologist rather than the surgeon.

It has long been my view that more deaths result from operations undertaken in the fear that an extradural hæmorrhage may be missed than from clinical extradural hæmorrhages. Unless the operation does positive good it does harm. Neurological factors may cause fatal pulmonary lesions, especially acute pulmonary œdema and bronchopneumonia. Unless the indications for operation are perfectly clear the patient should be left quiet.

The high mortality-rates quoted in your annotation of Oct. 17 are alarming. Neurosurgeons are few and far between. A keen local general surgeon and radiologist must be able to do better than this. The pathologist must report on all fatal cases and a special study should be made of those who had an operation which did no good.

Derbyshire Royal Infirmary, Derby. G. R. OSBORN.

LEUKÆMIA AND GEOGRAPHY

SIR,—In brief the thesis propounded by Dr. Phillips (Oct. 24) was: in 5 Western counties the death-rates from leukæmia rose to more than half as much again in 1954–57 compared with 1950–53, for which a possible cause is radiostrontium from "fallout". The only thing which saves this conclusion from ridicule is the word, possible. In the present state of knowledge of leukæmia virtually anything is possible, but the probability that the deduction is right must be infinitesimally small.

There is no doubt that a correlation exists. The rate of leukæmia has been rising in the past 8 years. Fallout of radiostrontium has also been increasing in the past 8 years. So have wages, but while Dr. Phillips summarily dismisses the one correlation, he adopts the other as probably causative.

If radiostrontium were causative the important factor would be the radiation-dose derived from the radiostron-

tium. This cannot be measured directly: it can, however, be calculated. If the isotope were uniformly distributed in bone salt (probably the most pessimistic assumption) the dose to bone and osteocytes would be some 2·5 mrad per year per strontium unit (1 $\mu\mu$C ^{90}Sr per g. Ca) and for bone-marrow some 3 times less. The dose to bone from natural radiation is some 150 mrad per year.

At the present time the degree of contamination of bone with ^{90}Sr is correlated with age. The published data of Bryant et al.[1] (1957–59) of analyses of bones (usually femurs) show values of about 0·2 S.U. for adults and about 1·5 S.U. for children about 1 year old. In children the contamination is homogeneous, in the adult not. Dr. Phillips' analysis does not allow for the age-factor.

Radiostrontium must irradiate bone-marrow, it is true, but only to a very minor extent lymph tissue. Dr. Phillips' analysis does not permit a breakdown of cases into myeloid and lymphatic types of leukæmia, or into acute and chronic forms.

For the thesis to be correct the relative effectiveness of the rad from radiostrontium would have to be orders of magnitude greater than that of the other components of natural radiation, which would be a unique situation. There are enough mysteries about leukæmia without adding this one.

The purpose of this letter, Sir, is therefore twofold:

(i) To see to it that Dr. Phillips' conclusion does not gain acceptance as dogma in any medical circle, however small, by default;

(ii) To state that, while I do not know the cause of the increasing incidence of leukæmia, not only in the last 8 years but in the previous 30 years, there is one thing of which the evidence convinces me—that it is not due to radiostrontium.

M.R.C. Radiobiological Research Unit, Harwell, Didcot, Berks. J. F. LOUTIT.

ACUTE ANOXIC CARDIAC FAILURE IN PULMONARY HEART-DISEASE

SIR,—Dr. Kellaway (Nov. 7) is to be congratulated on his article in which he rightly emphasised the importance of adequate oxygenation in the treatment of acute anoxic cardiac failure complicating pulmonary heart-disease. As he pointed out, the great problem is to administer a continuous and adequate amount of oxygen without causing CO_2 narcosis. To prevent this important complication of oxygen therapy he recommends intermittent injections of nikethamide and amiphenazole. During six and a half years in South Wales I had the opportunity of treating over 30 cases of coma due to acute respiratory failure after an exacerbation of chronic bronchitis.[2]

Virtually all the patients were miners, and many had evidence of cor pulmonale. After an initial intravenous injection of aminophylline (0·5 g.) and nikethamide (8 ml.), aminophylline (3·5 g.) and nikethamide (24 ml.) in 350 ml. of 5% dextrose was given by intravenous drip over every twelve hours. All patients were given continuous oxygen in an oxygen tent at a rate of 6–7 litres per min. At no time was there any evidence of CO_2 narcosis.

Penicillin (500,000 units intramuscularly six-hourly) and streptomycin (0·5 g. twice daily) were given as routine until the results of sputum culture were received. If the organism was sensitive, penicillin was continued for at least fourteen days and streptomycin for seven days. I find the usual five or seven days of antibiotics quite inadequate for these chronic bronchitics who have developed a superimposed acute respiratory infection. These short courses are often followed by recurrence of infection, often with rapidly fatal results.

In some of the more severely ill patients steroids are often lifesaving.

Amersham General Hospital, Bucks. M. S. PATHY.

SIR,—I consider Dr. Kellaway's article most enlightening. In the geriatric unit, especially during the winter, this problem is constantly seen. Dr. Kellaway made a very important point about continuous oxygen therapy coupled with respiratory stimulation. I would, however, be glad to know his opinion concerning the place of diuretics and steroids in this condition.

New Cross Hospital, Wolverhampton. KENNETH HAZELL.

UNSTABLE DIABETES

SIR,—Your leading article of Oct. 31 drew attention to the evidence suggesting that the hyperglycæmic rebound following hypoglycæmia is mediated by the release of adrenaline and glucocorticoids. In the following case spontaneous bilateral adrenal hæmorrhage was associated with hypoglycæmia and diabetes mellitus. It raises interesting speculations as to the ætiology and mechanism of such hæmorrhages.

A man of 71 had been a diabetic for 7 years and stabilised on 14 units of Novolente insulin and a 12-line diet. He became ill with abdominal pain and vomiting; urine testing by the family doctor revealed 2% glycosuria and heavy ketonuria; apart from this and a slight degree of hypertension (170/100 mm. Hg) there were no other physical signs.

The patient was immediately given 40 units of soluble insulin, and this was repeated in about 8 hours; the urine became free of sugar. Approximately 30 hours after the onset of his symptoms he became comatose and sweated profusely. After intravenous glucose, he was able to eat breakfast, but became comatose again in a few hours and he was admitted into hospital.

Apart from the coma, no physical signs were elicited, although it was noticed that abdominal palpation was resented by the patient. The blood-sugar was 68 mg. per 100 ml. and the blood-urea 59 mg. per 100 ml. Intravenous glucose did not produce any dramatic improvement, but later in the day, and for the following two days, he was rousable though confused. Next day the blood-sugar was 85, blood-urea 106 mg. per 100 ml., the urinary output poor, and the urine of high specific gravity. The next day blood-sugar estimations were 155 and 240, blood-urea 179 mg. per 100 ml., and serum-potassium 6·1 mEq. per litre; serum-sodium and serum-chlorides were normal. By this time there was complete anuria. The patient suddenly collapsed and died 48 hours after admission.

Postmortem findings.—Both adrenals were equally enlarged and spherical (diameter 4 cm.). The cut surface of each showed the centre replaced by a large blood-clot; the overlying cortex was for the most part intact, but there were small areas which had been replaced by hæmorrhage. The adrenal veins were free of thrombi. Apart from generalised pallor the kidneys appeared normal; there was no papillary necrosis. There was a small recent thrombus in a peripheral branch of the pulmonary artery to the right upper lobe. The remaining organs appeared normal.

Histology.—Sections from both adrenals showed a similar picture. The medulla had been completely replaced by recent hæmorrhage. In the cortex there were small areas of hæmorrhage, which in a few places had extended into the capsule and surrounding fat. The main lesion in the cortex, however, was a recent necrosis involving all zones, only small groups of cells in the zona glomerulosa appearing normal. The general architecture of the cells in the zona fasiculata was still recognisable but details of the individual cells were lost; the cells were vacuolated and empty and bounded by a necrotic, eosinophilic cell wall. No thrombi could be seen in the veins. Fat stains

1. Bryant, F. J., et al. AERE HP/R 2353, AERE C/R 2583, AERE C/R 2816, AERE/R 2988.
2. Pathy, M. S. *Brit. med. J.* 1956, i, 803.

revealed almost complete absence of sudanophilic material in the cortex: the adrenal arteries and arterioles were normal. The kidneys showed a recent tubular necrosis, affecting both the proximal and distal portions of the nephron. No focal lesions of diabetic glomerulosclerosis were seen. The pancreas appeared normal.

Adrenal hæmorrhage in the adult is rare; and, excluding cases due to septicæmia, hæmorrhagic diseases, tumours, and trauma, Berte [1] found a total of 22 cases in the literature and added a further 2 of his own. I believe that the present case may be the first reported with hypoglycæmia and diabetes mellitus.

The mechanism of hæmorrhage in these cases is not clear, and it is hard to find any common underlying feature in the reported cases. Stimulation of the adrenal cortex has been suggested [2–4] as a possible factor in the causation of adrenal hæmorrhage. Massive adrenal hæmorrhage was reported after corticotrophin therapy for arthritis and ulcerative colitis.

Rich [5] postulated that the adrenal hæmorrhage is a sequel to other degenerative changes in the adrenal cortex after stress.

In 7 of the cases in Berte's series [1] thromboses of the adrenal veins were found; in 5 of these the hæmorrhages and thrombi were bilateral. In the present case neither macroscopic nor microscopic thrombi were found and it would be hard to decide whether such thrombi, if found, preceded or followed the hæmorrhages. The associated tubular necrosis does suggest the possibility of some underying vascular basis for the adrenal and renal lesions.

The initial factor may have been the hypoglycæmia, possibly caused by an unaccustomed large dose of soluble insulin. Although it is difficult to assess at what stage the actual adrenal hæmorrhage took place, I suggest that this report does support the view that prolonged adrenal stimulation is a factor in massive adrenal hæmorrhage.

Pathology Department,
Royal Alexandra Hospital,
Rhyl, North Wales. G. HEFIN ROBERTS.

THE GHANA MEDICAL SERVICE

SIR,—Any doctor contemplating working in Ghana should speak first with someone able to describe the obverse of the rosy picture painted by Dr. Belfield Clarke (Nov. 14).

I am but one of many who have returned from Ghana, not after a visit, but after passing through its transitional period of some years of preparation for, and achievement of, independence. It is no coincidence that the country is now crying out urgently for doctors. There are but a handful of British medical officers remaining in Government service—in general medical duties, only one with over 5 years' service, and a few more in specialist, public-health, and administrative posts. What are the reasons for this? Certainly not financial.

New legislation was introduced last year to bring the medical field under full political control, and the ultimate control of professional disciplinary matters in Ghana is now in the lay hands of the Minister of Health. The Act gives him power to direct the activities of the disciplinary committee, to quash their verdicts and to initiate or suppress proceedings leading perhaps to disqualification. The last chief medical officer, a Ghanaian of long service who had the courage to stand out for his principles against the political control of strictly professional matters, learnt one morning by press and radio announcement of his own resignation.

REPATRIATE.

1. Berte, S. J. *Ann. intern. Med.* 1953, **38**, 28.
2. Altschule, M. D. *New Engl. J. Med.* 1955, **253**, 191.
3. Green, R. C. *J. Amer. med. Ass.* 1953, **152**, 133.
4. Wilson, D. A. W., Roth, D. *ibid.* p. 230.
5. Rich, A. R. *Bull. Johns Hopk. Hosp.* 1944, **74**, 1.

REFORM OF THE LAW ON HOMOSEXUALITY

SIR,—Dr. Learoyd (Nov. 7) has done a real service by voicing the opposition that the great majority of doctors feel towards the Wolfenden report. In a recent book I wrote "The danger of government planning is that it allows those in authority to give to any intended action the verisimilitude of a carefully considered policy by appointing a committee whose report can be guaranteed to recommend exactly what they want to do". I had in mind the Goodenough committee on medical education, but the observation applies equally well to the Wolfenden committee. By evidence overloaded with the views of psychiatrists, and ignoring those of schoolmasters, scout leaders, and wardens of boys' clubs, the men who are most aware of the corroding influence of homosexuality, they produce recommendations so opposed to the views of normal people that they have been met with nation-wide opposition.

Mr. Kenneth Walker has attributed views to the Church and the medical profession that are the exact opposite of those held by these bodies. Dr. Waycott has carried the emotional appeal further. By addition he has produced the alarming total of 57 years of prison sentence awarded for homosexual offences—a gross injustice. By division he could have revealed a greater injustice, the disturbing fact that thirteen men, who in their time may have corrupted scores of boys who might otherwise have been loving husbands and happy fathers, have been deprived of liberty for no more than 7% of their lives.

London, W.1. HENEAGE OGILVIE.

HUMIDIFICATION FOR PATIENTS WITH TRACHEOSTOMIES

SIR,—We should like to refer to Dr. Burtles' letter of Oct. 31 and we would point out that the East blower-humidifier unit is not the same as the apparatus described under reference 7. The East blower-humidifier unit differs in a number of ways from the unit described by Dr. Spalding,[1] and we therefore think that your readers should know that the blower-humidifier unit referred to can only be obtained from us.

H. G. East & Co. Ltd.,
Cowley, Oxford. H. G. EAST.

LOBECTOMY FOR BRONCHIAL CARCINOMA

SIR,—In his excellent paper of Oct. 24 Mr. Belcher surveys the results of so-called "policy lobectomy" in a five-year follow-up. A five-year survival-rate of 37% is very promising. Of course cases of bronchial carcinoma in which it is possible to perform a radical lobectomy constitute a series of chosen favourable cases. If pneumonectomy had been performed, as advocated by many surgeons, a higher operative mortality would be expected, and a greater reduction of lung function in the surviving cases would ensue.

With a view to saving functioning lung tissue (especially in elderly patients with reduced lung function before operation) and partially inspired by Mr. Belcher's paper [2] of 1956, I have for the past eighteen months been practising "policy lobectomy". As I treat many elderly patients, more than 50% of the operations for lung cancer have been "policy lobectomies" or palliative lobectomies, operations which carry a low mortality (in my series, incidentally, no mortality). Mr. Belcher has produced figures showing that lobectomy is a sound and safe pro-

1. *Lancet*, 1956, ii, 1140.
2. *ibid.* 1956, i, 349.

cedure in the treatment of lung cancer. As a consequence, more elderly and old patients can have the benefit of surgical treatment.

Surgical Department A,
Frederiksberg Hospital,
Copenhagen, Denmark. ER. CHRISTENSEN.

CHRISTMAS FACTOR IN THROMBOTEST

SIR,—Professor Owren (Nov. 7) described a new method for the control of coumarin therapy. One of the advantages claimed for this method is that it takes into account changes in the level of Christmas factor (factor IX) during treatment. Yet, animal (ox or horse) brain extract, which is known to contain Christmas-factor activity,[1] is one of the four constituents of the reagent advocated. Accordingly, it seems impossible that the plasma clotting-times would be influenced by variations in the concentration of this factor which is already supplied in the reagent.

Whatever the virtue of the thrombotest proves to be, sensitivity to depressions in Christmas-factor levels should not be expected. This has proved to be the case by preliminary experiments on plasma from patients with Christmas disease.

Department of Hæmatology,
The Royal Infirmary, Manchester. F. NOUR-ELDIN.

PROCAINAMIDE AS A MUSCLE RELAXANT

SIR,—In his letter of Nov. 7 Dr. Phemister describes a trial of procainamide as a neuromuscular blocking agent and reports that a gratifying response was obtained in the first patient treated and that some improvement was observed in certain other patients with troublesome hypertonicity of skeletal muscle.

Dr. Phemister concluded from the improvement which followed, in the original case, a change from the erect to the supine position, that "hypertonicity was appearing in response to proprioceptive impulses from the muscles—i.e., the muscle spindles". Procainamide was employed to reduce spasticity because it was considered "that procainamide may lessen the 'irritability' of muscle by stabilising the muscle-cell membrane."

An alternative mechanism could be interference with the transmission of nervous impulses from the small, motor fibres (gamma fibres) which innervate the contractile substance of the muscle spindles.[2] The proprioceptive inflow from the muscle spindle increases in proportion to the disparity which exists between the length of the muscle spindle and the length of the muscle-fibre in which it is embedded. Neuromuscular blockade of the gamma efferent system promotes relaxation of the muscle spindle with a consequent reduction in this disparity and a reduction in the number of proprioceptive impulses dispatched from the muscle spindle.

That such neuromuscular blockade occurs with procaine hydrochloride is fairly well established, and procainamide and procaine hydrochloride have similar qualitative pharmacological actions.

The effects of procaine hydrochloride at the myoneural junction were shown by Harvey [3] on the decerebrate cat. After injection of procaine, the contraction of the tibialis anterior muscle on motor-nerve stimulation, and on acetylcholine injection, was reduced. Jaco and Wood [4] showed that acetylcholine production at the myoneural junction of the cat is depressed by procaine hydrochloride.

Matthews and Rushworth,[5] reporting on the relative sensitivity of muscle nerve-fibres, afferent and efferent, in the cat, stated that the small (gamma) motor fibres to the muscle spindles are more readily paralysed by procaine hydrochloride than either the proprioceptive sensory fibres or the large (alpha) motor nerves to the muscle-fibres.

If procainamide shares with procaine hydrochloride an effect on cholinergic transmission, blockade of the small (gamma) motor efferents, which are, of course, cholinergic, may explain Dr. Phemister's results.

Department of Materia Medica and
Therapeutics, University of Aberdeen. T. M. FORRESTER.

TREATMENT OF CEREBRAL FAT EMBOLISM

SIR,—I read with interest the paper by Dr. Harnett and his colleagues describing the survival of a patient after the application of modern methods of coma management.

I believe, however, with Sage and Tudor [1] that heparin or other anticoagulants should be used in the treatment of systemic fat embolism, and suggest that these drugs appear to exert their beneficial effect through some hitherto unrecognised specific action. I do not share the pessimism of Gardner and Harrison [2] that a clinical trial of heparin in human fat embolism is unjustifiable. In an experimental trial with rats these authors found that heparin accelerated and increased the number of deaths after experimentally induced fat embolism, and concluded that the use of heparin was not warranted. I have, however, treated 2 cases of cerebral fat embolism in which anticoagulant measures were successful.

The first patient did not recover consciousness after reduction of a dislocated hip and fracture of the tibia. Petechiæ appeared on the shoulders and fat was present in the sputum. A diagnosis of fat embolism was made and, after thirty-six hours, treatment with heparin (10,000 units six-hourly) began and continued for five days. In two days he became conscious and recovered fully in five days.

The second case followed multiple fractures of the pelvis and leg. Three days after the injury the patient collapsed and became semiconscious and drowsy. Petechiæ were present on the shoulders, and on the sixth day he was given phenindione ('Dindevan') 200 mg. in the first twenty-four hours (under the supervision of Dr. Ewan Cadman). His level of consciousness improved remarkably in thirty-six hours, and after three days he was fully conscious.

In both these cases the condition of the patient was deteriorating, and the diagnosis of fat embolism was supported by petechiæ across the upper trunk. Although regression of symptoms is known to occur spontaneously, it was felt that a fatal outcome was likely in these two cases.

The effect of heparin in "clearing" lipæmic plasma was described by Hahn [3] and clinical use in patients suffering from fat embolism was suggested by French et al[4]. The survival of three cases described by Sage and Tudor [1] and my first case (treated in 1955) supports the value and safety of heparin administration.

The beneficial effect of phenindione in the second case above is interesting, particularly since clinical improvement occurred although prothrombin activity did not fall below 46%. It seems that the action in fat embolism is not related to the effect on coagulation. Evidence is available that the coumarin series of drugs retards formation of atheroma.[5] Nichol et al [6] suggest that "the benefit from sustained anticoagulant therapy is due to effects other than lessened coagulibility of the blood and that the natural progression of atheromatosis may be interfered with".

1. Nour-Eldin, F. Fourth International Congress of Biochemistry, Vienna, 1958; p. 138.
2. Hammond, P. H., Merton, P. A., Sutton, G. G. *Brit. med. Bull.* 1956, **12**, 214.
3. Harvey, A. M. *Bull. Johns Hopk. Hosp.* 1939, **65**, 223.
4. Jaco, N. T., Wood, D. R. *J. Pharmacol.* 1944, **82**, 63.
5. Matthews, P. B., Rushworth, G. *J. Physiol.* 1957, **135**, 263.

1. Sage, R. H., Tudor, R. W. *Brit. med. J.* 1958; i, 1160.
2. Gardner, A. M. N., Harrison, M. H. M. *J. Bone Jt Surg.* 1958, **39B**, 538.
3. Hahn, P. F. *Science*, 1943, **98**, 19.
4. French, J. E., Robinson, D. S., Florey, H. W. *Quart. J. exp. Physiol.* 1953, **38**, 101.
5. Horita, A., Loomis, T. A. *J. exp. Med.* 1954, **100**, 381.
6. Nichol, E. S., Keys, J. N., Borg, J. F., Coogan, T. J., Boehrer, J. J., Mullins, W. L., Scott, T., Page, R., Griffith, G. C., Massie, E. *Amer. Heart J.* 1958, **55**, 142.

It seems reasonable to assume that this effect of oral anticoagulants in atherosclerosis may be similar to the apparent lipæmia " clearing " effect of both heparin and the coumarin drugs in fat embolism. The possibility may exist, therefore, not only of an effective treatment of established systemic fat embolism but also of the prophylactic administration of these drugs in severe skeletal injury in a dose adequate for a specific protective action but unlikely to affect coagulation and cause complicating hæmorrhage.

Further observation on the use of anticoagulant drugs in multiple injuries is required, and I would be interested to receive details of any further cases of fat embolism treated either with heparin or the coumarin drugs.

Department of Orthopædic Surgery
University of Liverpool. GEOFFREY OSBORNE.

IMIPRAMINE

SIR,—I was interested in the use of amylobarbitone as a sedative in one of the cases showing disturbed behaviour described by Dr. Brooke and Dr. Weatherly (Oct. 10). Imipramine is supposed by some research-workers to resemble chlorpromazine in its basic formula. I saw recently a recommendation [1] that chlorpromazine be used to control overactivity presumably due to imipramine. In this same article, overactivity from excess monoamineoxidase inhibitors (iproniazid, &c.), it was stated, should be controlled by rauwolfia compounds.

St. Luke's Hospital,
Armagh. D. G. MAYNE.

HEXAMETHYLENE 1-6 BISCARBAMINOYLCHOLINE BROMIDE

SIR,—In your issue of Oct. 24 Dr. Churchill-Davidson and his colleagues described an interesting clinical investigation of this substance as a muscular relaxant of the depolarising type. Since they quote some papers from this laboratory in a way which might lead to misunderstanding, I beg to be allowed a few remarks.

This substance was not synthesised by Klupp et al.[2] but, as stated in the first publication and also by Herzfeld and Stumpf,[3] it was first investigated by M. J. Cheymol [4] in Paris and we got it from the Österreichische Stickstoffwerke.

The statement of the manufacturers, as quoted by the British authors, cannot be based on the papers to which they refer, since Klupp et al. never affirmed that hexamethylene had pharmacological actions comparable with curare rather than with decamethonium. Herzfeld and Stumpf [3] were not concerned with the muscular action but with the fact that the drug is in itself an inhibitor of acetylcholinesterase and plasmacholinesterase and has no muscarine-like actions. It is true that in dogs and rats (but not in cats) a certain antagonism to neostigmine was observed, when hexamethylene had been acting on the muscles for a considerable period. It is also true that the clinicians quoted by your contributors and many others [5–8] stated that in man respiration returned more quickly when neostigmine was applied.

In my review [9] of the subject I have therefore concluded that " the action of dicarbaminoylcholine on the neuromuscular receptor is of a dual nature ". From the new observations on man it would seem that the depolarising action prevails.

Institute of Pharmacology,
University of Vienna. F. BRÜCKE.

1. *Amer. J. Psychiat.* 1959, **115**, 756.
2. Klupp, H., Kraupp, O., Stormann, H., Stumpf, C. *Arch. int. Pharmacodyn.* 1953, **96**, 161.
3. Herzfeld, E., Stumpf, C. *ibid.* 1955, **100**, 391.
4. Cheymol, J., Delaby, R., Najer, H., Gay, Y. *C.R. Acad. Sci.* (*Clerm. Ferr.*) 1952, **235**, 1711.
5. Bergmann, H. *Anæsthesist*, 1958, **7**, 137.
6. Krüger, G.-A. *Ärztl. Wschr.* 1958, **13**, 892.
7. Mayrhofer, O., et al. *Anæsthesist*, 1955, **4**, 174.
8. Meissner, F. M. *ibid.* 1957, **6**, 362.
9. Brücke, F. *Pharmacol. Rev.* 1956, **8**, 265.

SORE OVER THE SACRUM

SIR,—Any new idea is worth serious consideration if it offers the double chance of easing the burden of the nursing staff and at the same time making the patient more comfortable. A nursing problem which I do not think has received the attention it merits at consultant level is the superficial blister which appears on the skin over the sacrum, often causing excruciating pain, but which can be prevented or cured by diligent care and a deal of hard physical work from the nursing staff. This type of painful sore is quite different from the deep, painless, decubitus ulcers in paralysed patients or in those prostrate with serious illness or old age, which are caused by subcutaneous gangrene as a result of the ischæmia of pressure.

The relatively trivial but very uncomfortable " blister " is almost entirely attributable, I believe, to the common hospital practice of using an impervious sheet of rubber or polyethylene under the patient with nothing other than one, or two at the most, layers of cotton sheet to separate it from the skin. A patient with slight pyrexia and a moist skin in these conditions generates a 100% humidity in the cotton sheet interposed between his sacrum and the impervious rubber layer. This means that the cotton sheet adheres to the rubber (or polyethylene) and the patient adheres to the cotton, and an ulcer then starts in the same way that a painful blister starts on our heel if the skin is exposed to an unaccustomed spell of walking in a hot sweaty boot. Attempts by the nursing staff to dry the skin with alcohol and induce dry slipperiness with talcum powder are defeated as soon as the sweating sacrum is again placed on the impervious sheet.

A method of preventing bedsores, or of treating early sores, which is well-known to an older generation of surgeons in North America but which appears quite unknown in England, is to nurse the sacrum directly on a sheepskin with the wool against the patient's skin, and I imagine that any success by this method must be attributable to improved ventilation by the layer of springy wool which resists compression into a solid mass. I have no information as to what is done when the patient is incontinent other than that it is customary for each patient to have two sheepskins!

It is not difficult to imagine the expression on the face of an English hospital matron were a surgeon to order a dozen sheepskins for use in his wards; even my attempts to have a patient nursed on six layers of old blanket (folded) between the draw-sheet and the rubber sheet have met with flat refusal. In nursing dogma a painful sacrum is usually attributed to small wrinkles in the draw-sheet, and therefore anything between the cotton sheet and the rubber sheet which might become wrinkled is regarded as more important than having the sacrum perpetually in a hot turkish steam-bath.

A solution to the problem seems possible in technologies which are everyday matters in the packaging industry where wrappings for various products can be constructed which are totally impermeable to liquid water yet at the same time porous to water vapour. A membrane possessing these characteristics interposed between the patient's sacrum and the mattress would prevent destruction of the mattress by the spilling of urine bottles, but would allow free penetration by water vapour from the patient's skin. A fabric which seems highly suitable for this purpose is woven from nylon thread and is impregnated with P.V.C. These fabrics are capable of passing water vapour at the rate of 7–12 g. per sq. m. per 24 hours

in comparison with the almost total impermeability of rubber or polyethylene. I have tested one of these fabrics personally by sleeping on it and comparing it with the sensation of sleeping on the red rubberised sheet commonly used in hospitals. There is no question of the greater coolness of the sacrum on the vapour-permeable sheet and this is apparent even when the subject is non-febrile. Specimens of this material have now been in use in my hospital wards for four months, and the ward sisters prefer the new sheet to red rubber or polyethylene. It seems unlikely that I shall be able to pursue this investigation any further with the facilities at my disposal, but perhaps it may be of interest to others in a position to develop it.

Manchester. JOHN CHARNLEY.

ENZYME THERAPY AND ALLERGY

SIR,—Recent revival of "systemic" enzyme administration—i.e., buccal, parenteral, or enteric-coated forms of various depolymerases (histamines, proteases, esterases, and cytochrome)—was based on the presumption that deficiency of the particular enzyme was responsible for pathological changes. For example, cholinesterase was infused to correct a deficiency of the transport level of this enzyme in certain patients. The goal of enzyme therapy was "substitutive".[1]

Experiences with cholinesterase infusion [2] elicited the paradox that responses were beneficial even in patients whose plasma level of enzyme was already raised. Some clinical results from injected plasma-cholinesterase were said to be inexplicable [3] and so they remain.

Among these results was the relief of allergic manifestations, including many instances of penicillin-hypersensitivity urticaria.[2 3] Penicillinase, a "specific" amidase which inactivates penicillin, was later introduced, ostensibly on more rational grounds, for like purpose.[4] Meanwhile, it appeared that other enzymes with little or no amidase activity—chymotrypsin and alpha-amylase—would also abate penicillin reactions.[5 6]

The confusion is heightened by the fact that systemically administered enzymes known to offset hypersensitivity phenomena may in themselves engender allergic reactions (penicillinase, trypsin, chymotrypsin, and streptokinase-dornase).

An investigation to test the hypothesis that *any* systemically exhibited depolymerase may elicit antiphlogistic and/or antiallergic effects, has just been completed. Some results of this confirmatory investigation permit assignment of the therapeutic efficacy of depolymerising enzymes to certain aspects of their "polyelectrolyte" character.[7] This conclusion follows from the ancillary work of biochemists who state that certain aminoacid sequences are common to the prosthetic groups of all hydrolases, as well as from the otherwise unanticipated effect of the non-proteolytic depolymerase, alpha-amylase, which is the antiphlogistic equivalent (at least) of the currently used esterases (cholinesterase, chymotrypsin) and amidases (plasmin, erepsin, trypsin, and streptokinase).[6]

During this investigation tablets containing 10 Schenley units of penicillinase each, in a mannitol base, were given four times daily to 30 patients in whom benefit would have been anticipated from buccal trypsin, amylase, or chymotrypsin. Included in the penicillinase group were 8 patients with specific allergic conditions; 5 with rag-weed pollinosis (3 rhinitis and 2 asthma), 2 with rhus dermatosis, and 1 with penicillin-induced angioneurotic œdema. The remainder were patients with traumatic or infective inflammatory conditions. All the patients with allergic manifestations, as well as most of those with inflammations due to trauma or infection, showed some response qualitatively similar to that which would have been anticipated had alpha-amylase, chymotrypsin, or streptokinase been similarly given. As applied, the three latter appeared quantitatively more effective as evaluated in comparable groups, but no conclusions should be drawn from this impression because the group was small and there is as yet no manner of equating "unitages" as applied to different enzymes.

A presumably allergic reaction was noted to the buccal penicillinase itself. This was in a 28-year-old male who had fallen asleep, partially covered, on a beach, and sustained moderate sunburn of the flexor surface of both legs. The enzyme was given for its antiphlogistic effect, which did not emerge; instead, after the third tablet severe œdema and vesiculation of the ankles and extensor surface of the feet developed. This involved the unburned as much as the burned parts. The reaction persisted for two days after stopping penicillinase (fourth dose), and then rapidly subsided when buccal alpha-amylase was given. This patient, a laboratory technician, had had an unexplained eosinophilia for years but could not otherwise recall any allergic incident. It is apparent from this case that hypersensitivity to one particular buccal enzyme is not necessarily carried over to another.

Recent studies in this country have shown that its milk-supply has a high sporadic penicillin content and that penicillin hypersensitivity due to milk ingestion is not uncommon.[8] Part of the evidence for this is the response to penicillinase and the assumption of a specific activity of the enzyme. We are the last to minimise the hazards of any inadvertent source of this notoriously sensitising antibiotic, and the first to call for its removal. But, on the basis of our own findings that penicillinase may allay allergic manifestations which are due to incitants other than penicillin, we must ask that the case for the dispersion of milk-borne penicillin sensitisation be judged on evidence other than that of therapeutic response to penicillinase.

The investigation on enzymes was part of a study on wound-healing mechanisms supported at this hospital by the Bureau of Adult Hygiene, New York City Department of Health.

Division of Surgical Research,
Harlem Hospital,
New York City.

ROBERT D. BARNARD
CHARLES P. FELTON
BELARDINO LUPINI.

PRECORDIAL CATCH (TEXIDOR'S TWINGE)

SIR,—My thanks to Dr. Oski (Oct. 24) for calling attention to the fact that the "pain without a name" has been designated (with some misgivings) the "precordial catch".[9 10] I have since read Dr. Asher's description of the pain [11] which, independently described, is essentially identical with our descriptions. Dr. Asher's letter of Oct. 31 was delightful, though my wife was infuriated by the casual manner in which he serves fame to my colleague—leaving me with mere generosity.

I have recently received a reprint from Dr. Allison,[12] who described a pain similar to the "precordial catch" under the heading of "intercostal cramp". We certainly wish to acknowledge the similarity of Allison's earlier description. We continue to prefer the phrase "precordial catch" for the reasons mentioned by Dr. Asher—that it does not imply any causal notions.

Recently I received two letters which flatly stated that this mysterious pain was due to hiatus hernia. Both senders were internists. A psychiatrist friend of mine

1. Barnard, R. D., Mentha, J. W. *Science*, **107**, 195, 1948.
2. Barnard, R. D. *Lancet*, 1952, ii, 345.
3. Barnard, R. D., Stanton, H. T., Goldman, B. *Ann. Allergy*, 1953, **11**, 170.
4. Davis, G. M., Koch, R., Zimmerman, M. C. Enzymes in Health and Diseases. University of California, April 2–4, 1959.
5. Parsons, D. J. *Clin. Med.* 1958, **5**, 11.
6. Tojo, C., Bido, C., Tomasini, S., Barnard, R. D. *Ann. Allergy* (in the press).
7. Barnard, R. D. Polyelectrolytes. International Symposium on Macromolecules, Wiesbaden, 1959.
8. Zimmerman, M. C. *A.M.A. Arch. Derm.* 1959, **79**, 1.
9. Miller, A. J., Texidor, T. A. *J. Amer. med. Ass.* 1955, **159**, 1364.
10. Miller, A. J., Texidor, T. A. *Ann. intern. Med.* 1959, **51**, 461.
11. Asher, R. *Lancet*, 1959, ii, 359.
12. Allison, F. G. *Canad. med. Ass. J.* 1943, **48**, 36.

considers the pain to be emotional in origin. An orthopædist wrote to tell me that the pain is due to arthritis of the spine. I do not know the origin of the "precordial catch"—and will look forward to reading the article that clarifies the problem.

Chicago. ALBERT J. MILLER.

ORAL THRUSH IN INFANCY TREATED WITH NYSTATIN

SIR,—Dr. Graham's article of Oct. 17 prompts me to report a similar trial on newborn babies conducted with my colleague, Dr. V. Prokou, in the State and University Maternity Hospital Alexandra, in Athens.[1]

To ensure a completely blind trial we chose for the control group instillations of a solution of 10% sodium bicarbonate (4 drops after each feed). The sister who allocated alternate cases in two groups A and B did not know what the solutions A and B contained, and the doctor who recorded the results did not know to which group each baby belonged. Nystatin was prepared as a solution containing 100,000 units per ml., and four drops (about 20,000 units) were instilled into the mouth after each feed.

The results, after omitting the babies who left the hospital before the thrush had completely disappeared, were as follows:

Treatment	No. of cases	Response			Relapse
		1–4 days	5–9 days	10–21 days	
$NaHCO_3$	36	16	13	7	2
Nystatin	28	24	4	0	0

Our results confirm Dr. Graham's findings and show that even smaller doses of nystatin, if regularly instilled after each feed, cure the stomatitis due to *Candida albicans*. The cost of the treatment can thus be reduced.

Athens. S. A. DOXIADIS.

THE COCKETT/ELGAN JONES (ST. THOMAS'S) OPERATION

SIR,—Mr. Harold Dodd's very interesting letter of Oct. 24 raises a point of fundamental importance in the management of patients with venous ulceration. The well-tried conservative treatment of ulceration—that is, elastic compression, massage, and exercises—gives excellent results, provided the patient continues to wear support to the limb.

Mr. Dodd states that patients who have undergone the St. Thomas's operation "wear protection appropriate to their healed limbs" and in the article to which he refers[2] that the limb "if scarred" is protected "for years by elastic stockings."

May I ask Mr. Dodd what percentage of his patients need to wear elastic support to the limb after, say, a period of six months from operation?

London, W.1. G. M. LUNN.

*** Mr. Lunn's letter was shown to Mr. Dodd whose reply follows.—ED. L.

SIR,—I am sorry I cannot give a firm percentage figure in answer to Mr. Lunn's question. I asked the question of three experienced persons (two registrars and an outpatient sister) and all replied "fifty-fifty".

I divide these persons roughly into two groups, the younger up to 55, and those older. The former do well. I see them once a year or less often, and it is not often that they ask for renewal of their stockings (they may get them from their own doctors).

Over 55 the leg picture is complicated by arterial and blood diseases, diabetes, rheumatoid arthritis, obesity, a consitutional tendency to skin disease, and unbalanced nourishment, so I emphasise the value of the protective stocking.

I see a steady trickle of recurrences through traumatic incidents, with and without stockings, but seldom spontaneous ulceration. It is this unpredictable re-ulceration in spite of pressure bandages and stockings that often persuades unwilling patients to have their ankle perforating veins ligated.

The benefits of the procedure, apart from the reduction of re-ulceration, include a surprising restoration of mobility (a business woman of 62, "I can now run for a bus as well as walk"; and a public-schoolmaster's wife at 60, on a picture postcard, "I climbed this mountain today!").

With an assessment of the person, and a complete diagnosis of the venous condition, a well-performed Cockett/Elgan Jones operation is a first-rate supplement to the pressure bandaging which has obtained for 300 years since Harvey's time.

London, W.1. HAROLD DODD.

OCULAR LESIONS IN ONCHOCERCIASIS

SIR,—Budden [1] has refuted the views of Choyce [2] on onchocerciasis. Mostly Choyce is wrong because he does not accept evidence gleaned elsewhere, which means in 99% of endemic onchocerciasis areas; yet again, in places he may be right. He is wrong (and the orthodox views championed by Budden are certainly right) when he suggests onchocerciasis is not a common cause of blindness. If the epidemiology of the disease is related to the incidence of the anterior lesions of the cornea only (which are not in dispute) we cannot escape the conclusion that onchocerciasis is a major cause of blindness. Nevertheless, in the case of the posterior degenerative lesion, it has to be admitted that Choyce may be right.

Both authors ignore the subdivision of posterior segmental lesions into the inflammatory type, where microfilariæ die in the choroid or retina, and the degenerative, unrelated to the presence of microfilariæ in the eye.

Bryant, the first to describe a posterior lesion in onchocerciasis, describes a typical inflammatory one. Ridley described a circumscribed degenerative type, which he recognised as being something different and which he considered was specific in appearance. Following these descriptions complete confusion reigned as to what was what, until I was lucky enough to obtain pathological specimens in support of my clinical assessment that there are *two* different lesions.[3]

Obviously, with the inflammatory type, the incidence is likely to rise with the infectivity rate. This is Budden's only argument against Choyce's polemic. Few of his other arguments against Choyce's views on the nature of the degenerative type of lesion are relevant. By confusing the clinical pictures he confuses all.

While I myself doubt whether Choyce is on the right track in calling this lesion a familial abiotrophy, I cannot accept Budden's arguments as evidence against such a view. There is no doubt the degenerative type of fundal lesion we are describing is very similar to the posterior primary choroidal sclerosis described by Sorsby. The arguments against this ætiology are largely based on the fact that to date it has been discovered only in onchocercal

1. *Acta soc. pædiat. hellen.* 1958. **37.**
2. Dodd, H. *Lancet*, 1957, ii, 1249.

1. Budden, F. H. *Trans. R. Soc. trop. Med. Hyg.* 1958, **52**, 500.
2. Choyce, D. P. *ibid.* p. 112.
3. *Amer. J. Ophthal.* (in the press).

areas and onchocercal cases. I will not go into other technical differences since they are debatable. But they are many.

University Laboratory of Physiology, Oxford. F. C. RODGER.

EFFECT OF 3-PYRIDINEACETIC ACID ON SERUM-LIPIDS

SIR,—The additional observations by Galbraith et al.[1] to the preliminary report of Altschul et al.[2] on the induction of hypocholesterolæmia by nicotinic acid prompts us to report our results with 3-pyridineacetic acid (3-P.A.A.).

In a selected group of 30 subjects with degenerative vascular disease (maintained on their previous diet and treatment) who were given orally 1·5–2·5 g. per day of 3-P.A.A. for a month, we have observed a striking and constant reduction of serum-cholesterol level, more sustained and prompt perhaps than the fall observed with the same doses of nicotinic acid. 3.P.A.A. produced, moreover, fewer side-effects than nicotinic acid.

The mean reduction of serum-cholesterol (determined by the Sperry-Schoenheimer method at weekly intervals) in the subjects with a basal level of more than 220 mg. per 100 ml. were 16·7, 17·1, 22·6, and 31·4%; and in those with basal values of less than 220, the week-by-week reductions were 9·2, 10, 12·4, and 17·1%.

The decrease in serum-cholesterol concerned especially the esterified fraction and the β-lipoprotein cholesterol, with decrease in the ratio of β- to α-lipoprotein cholesterol. We observed also a proportional reduction of the serum-total-lipids and of the cholesterol/phospholipids ratio, and a big increase of the non-esterified fatty acids.

3-P.A.A. showed a less striking influence than nicotinic acid on the glucose-tolerance test. In some patients under continuous treatment with 1·5–2 g. of 3-P.A.A. daily, the serum-cholesterol levels were constantly maintained in the normal range. A return of the serum-lipid concentrations to the previous levels was observed 15–20 days after withdrawal of therapy.

We believe that 3-P.A.A. will prove better than nicotinic acid for the long-term treatment of atherosclerotic hyperlipæmia. Further studies are in progress in our Institute.

We wish to thank Lepetit S.p.a. for a generous supply of 3-P.A.A.

Istituto di Clinica Medica Generale e di Terapia Medica, University of Milan. G. RATTI E. DE FINA.

CHOLESTERYL ESTER FATTY ACIDS IN ATHEROMA AND PLASMA

SIR,—In your issue of Nov. 7, Dr. Sinclair complains that our paper of Oct. 17 gave no information how palmitoleic acid was separated from the oleic acid shown in tables III and IV. Our section on methods stated "the monoenoic-acid content was determined by the difference between the iodine value and the sum of the contributions due to polyunsaturated acids", and so our monoenoic-acid figures included both oleic and palmitoleic. We reported them as oleic in tables III and IV in order to indicate that our figures were calculated by using a molecular weight of 282. In tables I and II they appear as monoenoic only because we had to compare our results with those of Tuna et al.[3] who did separate oleic and palmitoleic. Our bulking of oleic and palmitoleic as oleic should be understood by any worker in this field who read our paper carefully (it is a common convention) and would not substantially mislead anyone else or affect our conclusions. To say that we thereby "add chaos to (our) admitted confusion" seems an exaggeration.

Dr. Sinclair also criticises our assumption that the dienoic acid we determined by alkali isomerisation is linoleic; he suggests it could be a dienoic acid to the "oleic" series (i.e., the position of the first double bond, counting from the methyl end, being in the 9–10 position); such acids are intermediates in the conversion of oleic to eicosa—5, 8, 11-trienoic acid, which accumulates in animals deficient in essential fatty acids. A characteristic feature in these animals is a rise in trienoic acid content.

We found no such rise in the cholesteryl ester fatty acids of atheromatous tissue and so would not have expected an accumulation of the intermediate dienoic acids large enough to account for a substantial part of the high dienoic acid content. We therefore decided that most of this would be linoleic, but conceded in our section on methods that some of it might not be.

Dr. Sinclair has raised an issue worthy of investigation but current biochemical knowledge leads us to expect most of our dienoic acid figure to be made up of linoleic. It is open to anyone who disagrees to provide experimental evidence for his view.

Biochemistry Department, Johnston Laboratories, University of Liverpool. G. A. J. PITT R. A. MORTON A. S. WRIGHT.

CONTINUOUS INTRAVENOUS SEDATION IN SEVERE TETANUS

SIR,—Tetanus is common in Nigeria and is likely to remain so until native midwifery improves and active immunisation is widespread.

Of 1315 medical inpatients in this hospital in 1956, 123 had tetanus, and the mortality was about 50%. Between January, 1958, and March, 1959, there were 202 cases of tetanus, with a mortality of 68%. Tompkins [1] reported 141 cases of neonatal tetanus between April, 1953, and August, 1956, with a mortality of 89·6%.

The following case illustrates a relatively simple method of treatment.

A Yoruba policeman, aged 29, was admitted ten days after a compound fracture of the right tibia and fibula. He had had 1500 units of antitetanic serum (A.T.S.) and a course of 'Seclopen.' Ten weeks later he developed pain in the neck and slight trismus, and within twenty-four hours tetanic spasms began. The incubation period could not be accurately estimated, but he might have acquired the infection in hospital. He was given 100,000 units of A.T.S. intravenously, crystalline penicillin ½ mega unit six-hourly for the next three days, chlorpromazine 100 mg. six-hourly, and sodium amylobarbitone gr. 3 six-hourly. Because of his trismus and difficulty in swallowing, an intravenous infusion of 4·3% glucose in 0·18% saline was started on the eleventh day of the tetanus.

It proved impossible to control the spasms by these measures, and within a week the fits became more frequent and prolonged. Temperature varied between 100° and 102°F. As the period of onset was less than forty-eight hours [2 3] and his temperature never fell below 100°F,[1] the tetanus was judged to be "severe." It was decided to use a central depressant given by continuous infusion. On the twelfth day, a polyethylene cannula was introduced into the inferior vena cava via the left long saphenous vein, and 2 g. of sodium-thiopentone in a litre of 4·3% glucose in 0·18% saline solution was delivered at the rate of 2 litres in twenty-four hours. Unconsciousness was produced and reflex spasms were abolished, only slight tonic rigidity remaining in the neck and limbs. It was possible to control the degree of unconsciousness and flaccidity by altering the rate of the drip.

He was nursed in a quiet room on a 'Sorbo' rubber mattress, and was turned every two hours, the mouth and pharynx being sucked out each time. Each day the foot of the bed was raised for a few minutes to encourage drainage of secretions.

1. Galbraith, P. A., Perry, W. F., Beamish, R. E. *Lancet*, 1959, i, 222.
2. Altschul, R., Hoffer, A., Stephen, J. D. *Arch. Biochem. Biophys.* 1955, 54, 558.
3. Tuna, N., Reckers, L., Frantz, I. D. *J. clin. Invest.* 1958, 37, 1153.

1. Tompkins, A. B. *Brit. med. J.* 1958, i, 1382.
2. Cole, A. C. E., Robertson, D. H. H. *Lancet*, 1955, ii, 1063.
3. Shackleton, P. *ibid.* 1954, ii, 155.

He was fed through a gastric tube with a mixture of 1 pint of milk, 2 switched eggs, 1 oz. 'Casilan', and 1 oz. glucose at the rate of 4 pints in each twenty-four hours. This provided, with the glucose in his drip, about 3000 calories a day.[4] He also had vitamins and prophylactic antimalarials in the feeds. To protect the chest during unconsciousness, penethamate hydriodide (1 mega unit twice daily) was given by injection. By this means serum-electrolytes were maintained in fair balance.

At intervals thiopentone was withheld from the drip, so that progress could be estimated and the patient enabled to cough up bronchial secretions. His temperature remained between 100° and 102°F during the next few weeks, but his spasms were at all times well controlled. On the thirty-fourth day of anæsthesia it was possible to stop intravenous sedation without increasing the tone of the abdominal muscles. During this period he had had a total of 55 g. of thiopentone. On a "weaning" sedation of gr. 3 of sodium amylobarbitone twice daily, he gradually recovered consciousness. He has remained well enough since for the surgical treatment of his fracture to be continued. At no time did he need supplementary oxygen and he was never cyanosed.

This case was managed throughout by the nursing staff and two surgical dressers, working one at a time, with only occasional demands on doctors or anæsthetists. The level of sedation was such that suction and turning did not provoke spasms, but respiration was not depressed.

The variety of reported methods suggests that no one regime is entirely safe or universally feasible in tetanus.

A polyethylene tube left in a vein for many days may induce thrombosis,[5] but we considered this a lesser risk than that of prolonged tetanic spasms, because non-irritant isotonic glucose in saline was to be infused, because the patient's water and electrolyte balance and hæmoglobin level were satisfactory, and because we have found that the tendency to venous thrombosis in bedridden Nigerians in Ibadan is far less than European experience would suggest.

Kelly and Laurence [6] and Brooks et al.[7] agreed that chlorpromazine was superior to mephenesin in controlling tetanic spasms. Cole and Robertson [8] reported that barbiturates may be potentiated by the action of chlorpromazine; and Bodman et al.[8] emphasised that chlorpromazine diminished bronchial secretion.

Curare with tracheotomy and positive-pressure respiration has been used with nitrous oxide,[9] but the bone-marrow became depressed after prolonged administration of the gas.[10] Variable results were recorded with thiopentone or curare; but there were dangers and skilful supervision was needed.[8 11–15] Batten [16] reported success in 1 case with thiopentone given continuously for fifteen days. Chlorpromazine is thought [6 17 18] to be very potent against spasms of tetanus but in our case it was ineffective even in large doses.

We are indebted to the nursing staff of the ward for their care with this patient, and to Dr. Ezi-Ashi, house anæsthetist, who often gave advice. The patient was under the care of Mr. Richard Batten, to whom we are grateful for permission to publish this account.

University College Hospital, Ibadan, Nigeria.

E. ADEOLU LAWSON
M. AKINTAYO BANKOLE
Medical Students.

4. Wilson, G., Care, A. D. *ibid.* 1955, i, 1303.
5. Indar, R. *ibid.* 1959, i, 284.
6. Kelly, R. E., Laurence, D. R. *ibid.* 1956, i, 118.
7. Brooks, V., Curtis, D., Eccles, L. *Nature, Lond.* 1955, **175**, 120.
8. Bodman, R. I., Morton, H. J. V., Thomas, E. T. *Lancet*, 1955, ii, 230.
9. Lassen, H. C. A., Bjørneboe, M., Ibsen, B., Neukirch, F. *ibid.* 1954, ii, 1040.
10. Lassen, H. C. A., Henriksen, E., Neukirch, F., Kristensen, H. S. *ibid.* 1956, i, 527.
11. Forbes, G. B., Auld, M. *Amer. J. Med.* 1955, **18**, 947.
12. Godman, H., Adriani, J. *J. Amer. med. Ass.* 1949, **141**, 754.
13. Forrester, A. T. T. *Brit. med. J.* 1954, ii, 342.
14. Galloway, W., Wilson, H. *Anæsthesia*, 1955, **10**, 303.
15. Gusterson, F. *ibid.* p. 300.
16. Batten, R. *Lancet*, 1956, i, 231.
17. Laurence, D. R. *Proc. R. Soc. Med.* 1958, **51**, 1000.
18. Adams, E. B. *ibid.* p. 1002.

POSITIONING OF PATIENT FOR INTRA-ARTERIAL INJECTION OF THE LEG

SIR,—We have found that intra-arterial injection of vasodilator drugs (e.g., acetycholine) is a valuable treatment for obliterative vascular disease. The technique of intra-arterial injection is seldom mentioned in textbooks, and this must discourage many people from trying it. The following position of the patient makes intra-arterial injection easier and safer, even under difficult circumstances (for example, in obese patients, or when a femoral artery is deeply situated):

With the patient supine, a hard pillow is put under the hip. The doctor sits on the side to be injected and the patient lets his leg hang by the side of the bed. Thus the hip is hyperextended and the thigh is rotated outwards and abducted. By these means the femoral artery is brought near the surface and lies stretched on a firm base. It becomes more easily palpable and does not recoil from the needle when it is inserted. After the injection the patient is asked to sit up and press a piece of cottonwool over the puncture wound.

By this technique we have given as many as 70 injections to one patient without provoking any local reaction or scar. This position might also be useful for performing arteriograms via the femoral artery.

Department of Medicine,
University of Debrecen,
Hungary.

J. HANKISS.

CHRISTMAS GIFTS FUND APPEAL

SIR,—I should like to remind your readers who have not yet responded to the President's appeal that it is our custom to distribute the gifts some days before Christmas.

I hope all who can will send their contributions marked "Christmas Gifts" to the Royal Medical Benevolent Fund, 37, St. George's Road, Wimbledon, London, S.W.19, as soon as possible.

F. A. JULER
Honorary Treasurer,
Royal Medical Benevolent Fund.

Parliament

Hospital Building Programme

IN a written answer Mr. DEREK WALKER-SMITH, the Minister of Health, announced that it was proposed to spend £31 million on capital development in the hospital service in England and Wales in 1961–62, compared with £25½ million for next year, 1960–61. He has asked hospital boards to complete the planning of a number of additional major projects. He said:

These include, in the sphere of new building, the start of a new St. Mary's maternity hospital in Manchester and a new mental-deficiency hospital in Northamptonshire, and further substantial phases of the new Cambridge teaching hospital, West Wales General Hospital, and Peterborough Hospital.

Large extensions proposed for existing general hospitals include a new medical block at the West Middlesex Hospital; maternity departments at the North Middlesex Hospital, and at the City General Hospital, Stoke-on-Trent; and a new surgical block at the Royal Gwent Hospital, Newport. New operating-theatres and a physiotherapy department are to be provided at St. James's Hospital, Leeds, and new operating-theatres at the London Hospital. There will be additions or improvements at the Westminster Hospital, the Royal South Hants Hospital, Southampton, Leicester General Hospital, Torbay Hospital, and the General Hospital, Birmingham. A new outpatient department is to be provided for University

College Hospital, London, and for Bristol Royal Infirmary. An outpatient department at Walton Hospital, Liverpool, included in the programme will be designed by the Ministry's design unit as the first of a number of development projects which will embody and demonstrate the Ministry's views on the design of hospital buildings and provide information about cost. Provision is also being made for alterations necessary on bringing the Royal Naval Hospital, Chatham, into civilian use when its use by the Royal Navy ceases in 1961.

There are a number of large projects in the field of mental health. They include a new psychiatric unit at Darlington Memorial Hospital; the first phase of a unit for longer-stay mentally ill patients at Crookhill Hall, near Doncaster; and additions or improvements to the Northgate (Morpeth), Royal Earlswood (Redhill), and Coldeast (Southampton) mental-deficiency hospitals. Some adaptations of wards and other improvements for the accommodation of severely subnormal children are to be carried out at Queen Mary's Hospital for Children, Carshalton, and a new reception unit, outpatient department, and research and teaching unit provided at the Fountain Hospital, Tooting.

Last year I informed the House that I was considering with the hospital boards concerned and in the light of advice from the University Grants Committee what dental hospital projects should be undertaken to increase the output of the dental schools, as recommended by the McNair Committee on the recruitment of dentists, in addition to the new dental hospitals at University College Hospital and Birmingham already in the Government's programme. Planning is now proceeding on schemes for this purpose at King's College Hospital, the London Hospital, and at the dental hospitals at Bristol, Newcastle, Leeds, and Manchester. Development at Liverpool is also being considered, and a new dental hospital will form part of the new teaching hospital at Cardiff for which an architectural competition is now in progress.

In addition I am considering other proposals from the hospital boards, and hope to announce shortly a further list of projects on which planning may now proceed.

Mr. JOHN MACLAY, the Secretary of State for Scotland, announced that it was proposed that capital expenditure on hospital building in Scotland should be of the order of £3·2 million in 1960–61 and £3·9 million in 1961–62. While the actual level of capital expenditure in the succeeding years could not yet be determined, he had asked the regional hospital boards to complete plans for the following major projects:

At the Royal Infirmary of Edinburgh, a new outpatient department and casualty accommodation and other specialised facilities. This would be the first stage of the reconstruction of the hospital, and would probably also include some new inpatient accommodation designed to facilitate the next stage of the reconstruction.

At the Western General Hospital, Edinburgh, a new outpatient and casualty department, the first stage in the reconstruction of the old part of this hospital.

At the Western Infirmary, Glasgow, a new outpatient and casualty department together with inpatient accommodation for casualties and orthopædic patients, again the first stage of a major reconstruction.

At Glasgow Royal Infirmary, new specialised facilities for treatment and research, new accommodation for some of the professorial departments, and a new ophthalmological department.

A new unit at Foresterhill, Aberdeen, beside the existing hospitals there, to contain many additional surgical beds and operating-theatres.

He hoped that it would be possible to complete the detailed planning of these projects in time for building to start by 1962 or 1963. These projects, together with the proposed new teaching hospital at Dundee the plans for which were now being prepared, were designed to provide a radical improvement and extension of the facilities available in the main Scottish teaching hospitals. Other projects in non-teaching hospitals were also being considered.

More New Bills

THE Government propose to introduce early legislation empowering local authorities to use privately run residential accommodation for old people and to make direct provision for meals for them. When time permits a Public Health (Miscellaneous Provisions) Bill is to be introduced to give general application throughout the country to provisions relating to public health which are scattered through private Acts promoted by local authorities in recent years.

QUESTION TIME

Shortage of Dentists

Mr. BARNETT JANNER asked the Minister of Health whether he was aware that there is a shortage of dentists in Britain, and that over 7000 more were needed to supply the normal requirements for dental treatment; and what steps he was taking to increase the number of schools for training dentists.—Mr. WALKER-SMITH replied: I am well aware of the shortage. The Government have accepted the recommendation in the report of Lord McNair's Committee on Recruitment to the Dental Profession that the annual output of dental schools in Great Britain needs to be expanded to produce at least 800 dentists who will practise in this country. Measures for putting this into effect are under way. Mr. JANNER: Is the Minister aware that this is a scandalous position, that the McNair Report was issued years ago, and that the recommendations for new schools were made very forcibly? Is he prepared to do something rapidly about it, and does he realise that it takes seven years before a new school can be put into operation?—Mr. WALKER-SMITH: We are going ahead with the construction of dental hospitals and dental schools, and we have one coming on in Birmingham, one at University College Hospital, London, and one in Cardiff, to name only three in the bigger centres.

Dr. EDITH SUMMERSKILL: In view of the grave shortage of dentists and the increasing incidence of dental caries, will the Minister be prepared to introduce inducement grants for potential dental students?—Mr. WALKER-SMITH: As a matter of fact, there is no shortage of recruits to the dental profession at the present time. It is really a matter of accommodation, and we are getting on as fast as possible.

Dr. SUMMERSKILL: In view of the serious position, could the Minister tell us whether dental hygienists are now being employed?—Mr. WALKER-SMITH: Yes, dental hygienists are being employed. I do not say universally, but in certain dental hospitals, such as the Eastman Hospital.

In answer to a question Mr. KENNETH THOMPSON, parliamentary secretary to the Ministry of Education, said that since 1951, when the number was at its lowest, there had been an increase of the equivalent of more than 300 full-time school dentists. In 1958 the number was over 1000, but twice as many were needed to provide a fully comprehensive service. The shortage could be overcome only by a general increase in the supply of dentists.

QUESTION TIME

Progress of Clean Air Act

In answer to a question Sir KEITH JOSEPH, parliamentary secretary to the Ministry of Housing and Local Government, said that the Clean Air Act was now fully operative. The effectiveness of the measures taken under it would be cumulative. The powers given to local authorities to create smoke-control areas were adequate, but the Minister would like them used more energetically. In England and Wales 104 smoke-control orders were in operation at the end of October, 69 others had been confirmed, and a further 59 had been submitted for confirmation. Smokeless zones could be established only under local Acts. Out of some 300 local authorities in the black areas, 183 had so far submitted five-year programmes.

Obituary

SAMUEL JAMES CAMERON

M.B., LL.D. Glasg., F.R.F.P.S., F.R.C.O.G.

THOUGH it is now some sixteen years since Professor Cameron retired from the regius chair of midwifery in the University of Glasgow, his memory in the medical school is still bright and some of his achievements have become legendary. He died, as we have already announced, on Oct. 29 at the age of 81.

He was educated at Mill Hill School, London, and at Glasgow University, where his father, Murdoch Cameron, also held the chair of midwifery. He graduated M.B. with commendation in 1901 and almost at once chose his father's specialty as his own. After holding gynæcological house-appointments in London and Glasgow, he became assistant to the regius professor of midwifery in Glasgow and lecturer in clinical obstetrics. In due course he was elected to the staffs of the Western Infirmary, the Glasgow Maternity and Women's Hospital, Belshill Hospital, Motherwell Hospital, and Perth Hospital.

In 1934 he succeeded Prof. J. M. Munro Kerr in the regius chair. He retired in 1943, and the following year the university conferred on him the honorary degree of LL.D. He was a foundation fellow of the Royal College of Obstetricians and Gynæcologists. He was a joint author of a *Manual of Gynæcology*, *Difficult Labour*, and *Uterine Hæmorrhage*, and edited several editions of the *Glasgow Manual of Obstetrics*.

W. C. A. writes:

"Professor Cameron brought to his work throughout a long life a keen, almost boyish, enthusiasm, which was infectious to those who worked with him—be they colleagues, nurses, or students. Though he achieved a large measure of academic distinction, he will also be remembered for his clinical gifts, his great diagnostic skill, and speed and dexterity in operating. These gifts he used to the full, and in a busy life areas as far apart as Perth, Lanarkshire, and Dumfries had the advantages of his vast clinical experience in organising and running their maternity and gynæcological services.

"There was, however, another side to his character—his love of the country, particularly his beloved county of Lanark, where he did much to stimulate interest in William Smellie. He was responsible for having Smellie's tomb renovated and preserved and Smellie's library housed in the county town. Later he was instrumental in establishing a maternity hospital in Lanark, and at his wish this was named the William Smellie Memorial Hospital.

"For many years his home was in Lanarkshire, where he enjoyed a very happy family life and took great pleasure in his many country pursuits. He was an enthusiastic fisher, an excellent shot, and a keen observer of all country interests; he was often to be seen at meets conversing with his many friends of all stations. One of his greatest joys was to entertain his colleagues and juniors at his house in Stobieside, where, with his wife and family, he was a perfect host. He was an avid reader, and his knowledge of the history of the County of Lanark and its families was unique: he took a great interest in the arts and his home contained many treasures, paintings, mezzotints, silver, and old furniture."

Professor Cameron is survived by his widow, a son, and three daughters.

Births, Marriages, Deaths

DEATHS

SMELLIE.—On Oct. 31, at his home, 8, Greenbank Drive, Liverpool, 17, John McIldowie Hope Smellie, M.B. Edin., in his 65th year.

Notes and News

CHRISTMAS CARDS

THE date of one summit at least has been fixed, and robins, reindeers, and holly are casting long shadows before them. If it is still a little too soon to think of stockings, it is already time to think of Christmas greetings to friends in distant parts and not too early to buy some cards for those at home. Good causes are again offering their cooperation at this season of goodwill, and the following have asked us to remind our readers of their cards:

The Imperial Cancer Research Fund (Lincoln's Inn Fields, London, W.C.2) has five reproductions of paintings and drawings by Miss Anna Zinkeisen at prices ranging from 1 guinea to 9*s.* per dozen. The United Nations Children's Fund (14, Stratford Place, W.1) has a new series of five cards designed by Bettina, a British artist who illustrates children's books, and other cards by artists from Denmark, Hungary, the United States, and Spain. They are all sold in boxes of ten for 7*s.* 6*d.* The National Association for Mental Health (39, Queen Anne Street, W.1) is offering cards from 9*s.* 6*d.* to 4*s.* 6*d.* per dozen and an assorted pack of eighteen for 10*s.* Their new designs for this year include *Four Geese Carolling* and the Elder Brueghel's *Adoration of the Kings*. The National Marriage Guidance Council (78, Duke Street, W.1) has cards from 4*s.* to 12*s.* a dozen including an unusual and attractive engraving of the *Nativity* by Willi Harwerth and a brilliantly coloured design of the *Three Kings* by Barbara Jones. The Grenfell Association (66, Victoria Street, S.W.1) is fortunate in sharing such professional appurtenances as snow and sledges with Father Christmas. Their Labrador pictures are never so appropriate as at this time of year, and besides cards (3*d.* to 9*d.* each) they offer "polar bear" stationery, tie-on gift labels, calendars, and bookmarks. The Chest and Heart Association (Tavistock Square, W.C.1) is selling sets of Christmas seals, depicting British birds, at 5*s.* a sheet of sixty.

COMMONWEALTH FUND

DURING 1958–59 this American Fund [1] has made grants of nearly $4 million. By far the largest part of this sum (84%) was given to projects for the promotion of health. The chief concern of the Fund has been to strengthen medical teaching and to promote better and more comprehensive health care, and medical education and community health activities received grants of $1,354,000. Help in the development of American medical schools is the chief activity of the Fund at present. During the past year what has been achieved by the medical schools with its help has been reviewed. This appraisal has not been agonising and has encouraged the Fund to continue to concentrate its support on new approaches to the better teaching of comprehensive medicine and to patient care. In future somewhat fewer grants may be made for mental-health work, but the Fund does not expect to withdraw completely from this field. The Fund believes that medical education, and activities closely associated with it in university education, are of strategic importance in the future of health service, and it is offering further grants to the Association of American Medical Colleges and to individual medical schools to study such aspects of the teaching-learning process as student selection, medical school progress in relation to college grades, personality characteristics of medical students, and objective measures of medical ability and proficiency.

ORGANISATION PSYCHIATRY

EMOTIONAL strains are as big a hazard to the psyche of the organisation man as the bandsaw is to the fingers of the carpenter, and mental and emotional disorders can account for as much absence from work, inefficiency, and probably accidents as can physical disorders; and yet industrial psychiatry is still in its infancy.

The division of organisation psychiatry of Mount Sinai Hospital, New York, which began work last December,[2] can call on the services of ninety psychiatrists—said to be the largest psychiatric attending staff at any American general

1. Annual report for 1959, obtainable from the offices of the Fund, 1 East 75th Street, New York 21, N.Y.
2. See *New York Times*, Nov. 1, 1959.

hospital—and a 123-bed psychiatric unit will be included in the hospital's new building, to be ready in January, 1961. Directed by Dr. Milton R. Sapirstein, the division has two chief functions—the provision of psychiatric services to corporate employees, and research in industrial psychiatry.

It has received grants from a distilling company and from the New York Foundation; and Health Insurance Plan of Greater New York has subscribed to an investigation of insurance for psychiatric services. Besides its initial grant the distilling company pays the division a flat fee for diagnostic consultation services to patients referred by the company's medical department; the division will also arrange treatment, for which a separate charge is made. Other firms have expressed an interest in this scheme. Other services to the company include the division's current studies of the disturbances associated with retirement and means of easing them, and of the relation between aptitude testing and the subsequent performance of those tested. Dr. Sapirstein believes that the fact that the assessment of tests and performance is made by a body with no direct interest in the results will protect the interests of the individual. Further studies contemplated include the treatment of alcoholism.

This extension of industrial medicine will fill a gap not only for executives but also for the worker at the bench, desk, or coal-face; and the close cooperation between a firm and an enthusiastic general hospital with a large psychiatric department may prove a useful model for future enterprises.

NEW FILM ON CHILDBIRTH

A NEW film, *Naissance* [1] (35 mm., sound, black-and-white and colour, 35 minutes, France), intended for showing to patients attending antenatal classes, was presented in London recently by Dr. Pierre Vellay.

It shows the procedure adopted by Dr. Lamaze at the Pierre Rouques Clinic in Paris for achieving painless childbirth by antenatal instruction, in accordance with the theories of Pavlov. The first half shows the course of instruction given to expectant mothers, with special reference to the role of the mind in relieving the pains of labour, and the second part—which is in colour—shows the management of the delivery of a mother having her third baby.

This is a new version of Dr. Lamaze's own film, *Painless Childbirth* (16 mm., sound, black-and-white, 21 minutes, France 1954 [2]). The anatomical and physiological descriptions of pregnancy and labour are helped by useful diagrams, and the importance of relaxation exercises and the control of respiration is stressed. The delivery, which occupies thirteen minutes of screen time, looked like an average multiparous second stage, and, though the mother was seen to be inhaling gas from a mask, we were assured that this was only oxygen—its purpose was not discussed. These films, and Dr. Vellay's book,[3] indicate the importance of antenatal classes to those who rely exclusively on analgesics in labour.

University of Aberdeen

The University Court announced on Nov. 12 that they expected to receive £50,000-£60,000 as residuary legatee of the estate of Mr. J. W. A. Hunter, a Manchester gynæcologist, to establish medical scholarships.

Mr. Hunter laid down the conditions that the parents and grandparents of the scholars must all have been born in Scotland and that the scholars must not smoke while holding the award. The scholars are to be selected not only by a competitive examination, but also with due regard to the assessment of their character and general attainments, including athletics.

Dr. James Crooks has been appointed senior lecturer in therapeutics in the department of materia medica.

University of St. Andrews

Dr. A. S. Todd has been appointed lecturer in pathology in Queen's College, Dundee.

Royal College of Physicians of London

On Tuesday and Thursday, Dec. 8 and 10, at 5 P.M., at the college, Pall Mall East, S.W.1, Dr. W. S. C. Copeman will give the FitzPatrick lectures. He will speak on the scientific basis of Tudor medicine and diagnosis, disease, and treatment in Tudor times.

1. Further information on the film may be obtained from The Editor, *Family Doctor*, B.M.A. House, Tavistock Square, London, W.C.1.
2. See *Lancet* 1955, i, 1231. Copies available from Plato Films Ltd. 18, Greek Street, London, W.1.
3. Childbirth without Pain. London, 1959.

Royal College of Surgeons of England

At a meeting of the council on Nov. 12 with Sir James Paterson Ross, the president, in the chair, Lord Kindersley was admitted to the honorary fellowship. Prof. A. G. R. Lowdon and Prof. A. W. Wilkinson were elected to the fellowship *ad eundem*. The Lady Cade medal was presented to Group-Captain W. B. Thorburn.

A diploma of fellowship was granted to G. R. Parry and licences to practise and postgraduate diplomas were conferred on those named in the report of the comitia of the Royal College of Physicians in our issue of Nov. 7 (p. 798).

Royal College of Physicians of Ireland

The following officers have been appointed:

President, Dr. P. T. O'Farrell; vice-president, Dr. Anna M. E. McCabe; censors and examiners, Dr. E. B. McEntee, Dr. A. Whelton, Dr. E. W. L. Thompson, Dr. Anna M. E. McCabe; representative on the General Medical Council, Dr. E. T. Freeman; registrar, Dr. Charles Dickson; treasurer, Dr. Geoffrey Bewley.

The following were admitted to licentiateship and membership of the college:

J. T. Cassidy, Deborah M. T. Cronin, J. G. Devlin, P. J. R. B. Keelan, J. T. Leahy, Maire MacCormac, T. A. M. Staunton.

Society of Apothecaries of London

Faculty of the History of Medicine and Pharmacy.—Canon Charles E. Raven will give the inaugural lecture of this Faculty in the hall of the society on Wednesday, Dec. 2, at 8.30 P.M. He is to speak on Medicine—Mother of Sciences.

The Faculty is organising the first British Congress on the History of Medicine to be held in London on Sept. 29 and 30. The theme of the congress will be the evolution of British medical practice. The Faculty is also compiling a panel of lecturers. Forms of application for membership and for inclusion on the panel may be had from the hon. secretary, Dr. F. N. L. Poynter, Wellcome Historical Medical Library, Euston Road, N.W.1.

College of General Practitioners

Today, Saturday, Nov. 21, at 11.30 A.M. at B.M.A. House, Tavistock Square, London, W.C.1, Dr. J. A. L. Vaughan Jones will give the James Mackenzie lecture. He will speak on the general practitioner and industrial health.

Chadwick Trust

On Thursday, Dec. 10, at 5 P.M., at St. Mary's Hospital, London, W.2, Dr. F. R. Bettley will give this Trust's Malcolm Morris lecture. He will speak on skin hazards of today.

Pharmaceutical Society of Great Britain

On Thursday, Dec. 3, at 7.30 P.M., at 17, Bloomsbury Square, London, W.C.1, Dr. Harold Jackson will give a lecture on antifertility substances.

Royal Society

One of the Royal medals of this society has been awarded this year to Prof. P. B. Medawar for his work on tissue transplantation immunity and acquired tolerance.

World Health Organisation

Dr. M. G. Candau has accepted the World Health Assembly's offer to extend his term of office as director-general of W.H.O. till 1963.

Association of Anæsthetists of Great Britain and Ireland

This Association is offering a prize of 200 guineas for the best essay on original work on general anæsthesia for dental surgery.

An Association of Clinical Psychiatrists

The first general meeting of the Group for Representation of the Views of Clinical Psychiatrists (G.R.V.C.P.) was held in London on Oct. 2. It has been formed to discuss the implications for psychiatry of the new Mental Health Act. Further particulars may be had from the chairman, Dr. J. T. Hutchinson, Cane Hill Hospital, Coulsdon, Surrey, or from the hon. secretary, Dr. R. W. Crocket, 13, Balgores Crescent, Romford, Essex.

International Congress on Medical Records

This congress will be held in Edinburgh from April 25 to 29. Sir Kenneth Cowan will give the opening address; and further particulars may be had from Miss E. M. Beeby, Royal Infirmary, Hull, Yorkshire.

British Association of Physical Medicine

The annual meeting of this association will be held on April 29 and 30, at King's College Hospital, Denmark Hill, London, S.E.5. The meeting will include a discussion on metabolic diseases affecting the locomotor system, and the opening speakers will be Dr. R. M. Mason, Dr. Stephen Mattingly, Dr. John Anderson, and Dr. A. M. Rackow.

Association of Cancer Institute Directors

The directors of cancer research institutes in America have formed this Association, which is composed of the senior scientific executives of institutions and autonomous divisions and departments, to encourage the exchange of ideas, information, personnel, and special facilities between groups with predominant interests in cancer, and to guide lay organisations about research, education, and the care of cancer patients. The Association will, in the future, consider members from among the scientific directors of cancer institutes of foreign countries. The first meeting was held in October when Dr. George Moore, director of the Roswell Park Memorial Institute was elected president. Dr. R. Lee Clark, Jr., director and surgeon-in-chief of the University of Texas M. D. Anderson Hospital and Tumour Institute, Houston, Texas, is the secretary-treasurer of the new Association.

On Nov. 7 the honorary degree of doctor of the University of Grenoble was conferred on Mr. H. J. Seddon.

Mr. Derek Walker-Smith, the Minister of Health, has appointed Mr. R. G. Cooke as his parliamentary private secretary.

A fellowship for poliomyelitis research has been established in the department of medicine at Birmingham University by the Jeff Hall Memorial Fund. The first scholarship has been awarded to Dr. S. C. Melnick.

On Thursday, Dec. 3, at 7 P.M. at 16, Princes Gate, London, S.W.7, Sir Stanford Cade will speak to the medical group of the Royal Photographic Society on What I Want from a Medical Photograph.

Operation of Sterilising Autoclaves—A report of the symposium on this subject, which was held in Brighton in May (see *Lancet*, 1959, i, 1055), has been published by the Pharmaceutical Press, 17, Bloomsbury Square, London, W.C.1 (pp. 45. 7*s.* 6*d.*, postage 4*d.*).

Appointments

COUTTS, VERA C., M.B. Aberd., D.P.H.: assistant M.O., Perth and Kinross Joint County Council.
FARQUHAR, J. V. L., M.R.C.P.E., D.P.H.: district M.O.H., Northamptonshire (Kettering).
*HAMILTON, J. G., M.D. Lond., F.R.C.S., M.R.C.P.: part-time consultant neurosurgeon, Midland Centre for Neurosurgery.
HERDMAN, PATRICIA, M.B. Lond., D.P.H.: senior M.O., Buckinghamshire.
HETHERINGTON, SUSAN, M.B. Manc.: assistant M.O.H. and school M.O., Blackburn.
McDONALD, JOHN, M.B. Glasg., D.P.M.: assistant psychiatrist (S.H.M.O.), Perthshire mental hospitals.
McNEILLY, WENDY I., M.B. Birm: assistant M.O.H., Walsall.
*NEWTON, E. J., M.B. Madras, F.R.C.S.: part-time consultant neurosurgeon, Stoke-on-Trent group of hospitals and Midland Centre for Neurosurgery.
O'SULLIVAN, E. P., M.B. Sydney, D.C.H.: house-physician, The Hospital for Sick Children, Great Ormond Street, London.
THOMAS, PATRICIA I., M.B. Lond., D.OBST., D.C.H.: assistant M.O., Middlesex (area 10).

Colonial Appointments:

BOARDMAN, H. M. S., O.B.E., L.R.C.P.E.: D.M.S., Sierra Leone.
CARTER, F. S., M.D. Cantab., D.C.H.: medical specialist, Aden.
DARLING, J. S., O.B.E., M.B. Belf., F.R.C.S.: specialist surgeon, Uganda.
ELLIS-JONES, D. W., M.B. Lpool, D.T.M. & H., D.O.: senior specialist, Uganda.
HARBEN, E. F., M.B. Madras, D.T.M. & H., D.P.H.: M.O. (special grade), Sierra Leone.
LOVETT, W. C. D., O.B.E., M.D. Lond., D.P.H., D.T.M. & H.: A.D.M.S., Tanganyika.
ROBERTSON, D. H. H., M.B. Edin., M.R.C.P.E., D.T.M. & H.: senior medical research officer (grade II), East African trypanosomiasis research organisation, East Africa High Commission.

* Amended notice.

Diary of the Week

NOV. 22 TO 28

Monday, 23rd

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Dr. Brian Ackner: Principles of Simple Psychotherapy.
LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE, Keppel Street, W.C.1
5.30 P.M. Sir John Charles: Research and the Public Health. (First Hope Clark lecture.)
MANCHESTER MEDICAL SOCIETY
9 P.M. (Medical School, University of Manchester.) *General Practice.* Dr. A. Cooke: On Making Mistakes.
UNIVERSITY OF ST. ANDREWS
4 P.M. (Department of Medicine, Queen's College, Dundee.) Dr. K. G. Lowe: Disorders of Renal Tubular Function.

Tuesday, 24th

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8 P.M. *Medicine.* Air Commodore W. K. Stewart, Squadron-Leader Peter Howard, Dr. D. M. Kerslake, Wing-Commander P. D. G. Whittingham, Wing-Commander Frederick Latham: Medical Problems of High Speed Travel.
POSTGRADUATE MEDICAL SCHOOL
4 P.M. Dr. E. H. Belcher: Radioisotopes in the Study of Blood Circulation.
ST. MARY'S HOSPITAL MEDICAL SCHOOL, W.2
5 P.M. Mr. V. B. Green-Armytage: Repeated Abortion.
ROYAL ARMY MEDICAL COLLEGE, Millbank, S.W.1
5 P.M. Mr. F. A. D'Abreu: Aspects of Pancreatic Surgery.
ROYAL STATISTICAL SOCIETY
5.30 P.M. (London School of Hygiene and Tropical Medicine.) *Medical section.* Mr. R. D. Clarke: Recent Trends in Mortality.
LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5.15 P.M. (General Infirmary at Leeds.) Prof. J. M. Cumings: Cerebral Lipidoses.
UNIVERSITY OF DUBLIN
4.30 P.M. (Trinity College, Dublin.) Prof. W. Melville Arnott: Respiratory Failure. (Frederick Price lecture.)

Wednesday, 25th

POSTGRADUATE MEDICAL SCHOOL
2 P.M. Prof. D. A. K. Black: Gastric and Intestinal Funcion.
INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. R. W. Riddell: Recent Advances in Immunology of Mycotic Infections.
INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. R. V. Gibson: Constrictive Pericarditis.
ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland, Place, W.1
3.30 P.M. Dr. Eileen Ring: Health Education in the Maternal and Child Welfare Services.
WEST LONDON MEDICO-CHIRURGICAL SOCIETY, West London Hospital, Hammersmith, W.6
8.30 P.M. Dr. W. S. C. Copeman, Dr. Redvers Ironside, Dr. Geoffrey Konstam, Dr. L. P. E. Laurent: Recent Advances in Medical Treatment.
ROYAL COLLEGE OF PHYSICIANS OF EDINBURGH, 9, Queen Street, Edinburgh
5 P.M. Prof. Sheila Sherlock: Hepatic Failure. (Sydney Watson Smith lecture.)
UNIVERSITY OF ST. ANDREWS
2.30 P.M. (Department of Medicine, Queen's College, Dundee.) Dr. W. K. Stewart: Œdema, Sodium, and Water.

Thursday, 26th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Mr. N. R. Barrett: Anatomical and Pathological Considerations Concerning Multiple Hydatid Cysts in the Chest. (Arris and Gale lecture.)
ROYAL SOCIETY OF MEDICINE
5.30 P.M. *Library* (*Scientific Research.*) Mr. C. C. Stevens: Copyright.
POSTGRADUATE MEDICAL SCHOOL
4 P.M. Dr. T. Alper, Dr. M. Ebert, Dr. R. H. Thomlinson: Biological Effects of Radiation.
INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. O. L. S. Scott: Erythemato-squamous Eruptions.
INSTITUTE OF PSYCHIATRY, Maudsley Hospital, Denmark Hill, S.E.5
5 P.M. Sir Rudolph Peters: Convulsive Conditions and Enzyme Biochemistry.
MANCHESTER MEDICAL SOCIETY
8 P.M. (Medical School, University of Manchester.) *Anæsthetics.* Dr. V. J. Keating: Metabolic Reaction to Surgery in Coloured Patients.
UNIVERSITY OF ST. ANDREWS
5 P.M. (Physiology department, Queen's College, Dundee.) Prof. D. H. Collins: Dysplasias and False Tumours of Bone.

Friday, 27th

ROYAL SOCIETY OF MEDICINE
8.15 P.M. *Obstetrics & Gynæcology.* Dr. Raoul Palmer (Paris), Mr. Armytage: Modern Methods of Salpingostomy.
POSTGRADUATE MEDICAL SCHOOL
10 A.M. Mr. J. H. Peacock: Raynaud's Disease and Acrocyanosis.
4 P.M. Prof. J. H. Kellgren: Pain and Disability.
MEDICAL SOCIETY FOR THE STUDY OF VENEREAL DISEASES, 11, Chandos Street, W.1
7.30 P.M. Dr. R. D. Catterall: Collagen Disease and the Chronic Biological False Positive Phenomenon.
INSTITUTE OF NEUROLOGY, National Hospital, Queen Square, W.C.1
4.45 P.M. Dr. Marion C. Smith: Neuropathological Material Considered in Relation to Neuroanatomy.
INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
3.30 P.M. Mr. S. E. Birdsall: Diseases of the External Auditory Meatus.
UNIVERSITY OF DUBLIN
5 P.M. (Trinity College, Dublin.) Mr. L. B. Somerville-Large: History of Ophthalmology in Ireland. (Montgomery lecture.)